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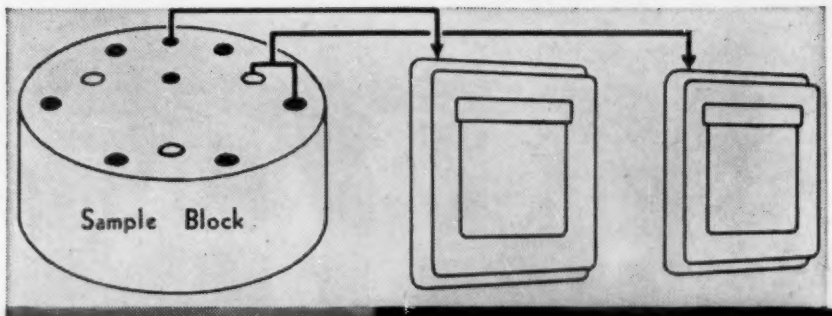

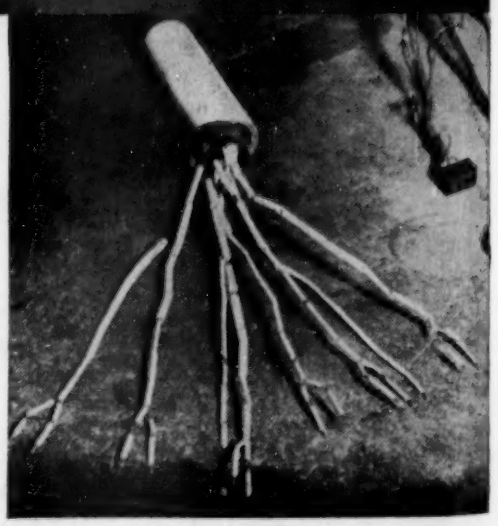

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* *Kulp, J. L., Kerr, P. F., Science, Vol. 105, p. 413, 1947.*

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On the Nomenclature of the Anti-Rh Typing Serums:

Report of the Advisory Review Board

William B. Castle, Maxwell M. Wintrobe, and Laurence H. Snyder *(Chairman)*

AT THE REQUEST OF THE SURGEON GENERAL of the U. S. Public Health Service, the Review Board convened in Washington on October 20 and 21, 1947. Formal evidence bearing on the question of the nomenclature of the anti-Rh typing serums was presented by 8 of the outstanding producers and users of such serums in the United States. Informal statements and discussions were offered by several others of the large group present at the hearing.

Two systems of nomenclature stand out above all those which have been proposed, and these two systems are in wide use. One of the systems is based on the series of allelic genes proposed by Wiener; the other, on the series of three closely linked pairs of genes proposed by Race and Fisher, of England. A comparison of the individual antiserums of the two systems would be as follows:

Wiener	*Fisher-Race*
Anti-rh′	Anti-C
Anti-Rh_0	Anti-D
Anti-rh″	Anti-E
Anti-hr′	Anti-c
Anti-Hr_0	Anti-d
Anti-hr″	Anti-e

Combinations of two or more antiserums have special designations on the Wiener system. A comparison of some of these would be:

Wiener	*Fisher-Race*
Anti-Rh_1 (Anti-Rh_0′)	Anti-C + D
Anti-Rh_2 (Anti-Rh_0″)	Anti-D + E

The antigens involved are genetically determined, and therein lies the reason for the formulation of two distinct systems of nomenclature. Antigen Rh_0 (antigen D) was the first to be discovered (Levine and Stetson, *9*; Landsteiner and Wiener, *3*). It was quickly shown by Wiener and his co-workers to be inherited on the basis of a dominant gene; that is, a child does not have antigen Rh_0 unless one or both parents have it (*4, 26*). This fact is not questioned by any reputable worker and may be considered as established.

The original antigen Rh_0 was demonstrated in 1940 by means of immune animal serums. As soon as the relationship of this antigen to erythroblastosis was discovered (*8*), however, it became clear that the best available sources of potent antiserums are human patients—either the mothers of erythroblastotic infants or persons immunized by transfusion of incompatible blood. The use of such antiserums gave rise to the discovery that there are other types of antigens in human erythrocytes, obviously related to antigen Rh_0 but not identical with it. Whereas antigen Rh_0 occurred in 85% of the white population of New York, one of the new antigens demonstrable by the serum of a patient who had experienced hemolytic transfusion reactions occurred in only 70% of the population (*7, 17*). This antigen, called Rh′, was later renamed rh′, the small letter being used because this antigen was found to be less important clinically than Rh_0. About 87% of the white population of New York appeared to possess one or the other or both antigens, and serums containing both antibodies were found by Levine.

Like antigen Rh_0, rh′ never appears in a child's blood unless it was present in the blood of one or both parents (*25*). What, then, is the genetic relationship of antigens Rh_0 and rh′? The genes responsible must be either independent, linked, or allelic. Considering, in a manner similar to that known to be involved in the A-B blood groups, a gene for antigen Rh_0, a gene for antigen rh′, and a gene or genes for neither antigen, Wiener showed that none of these explanations was satisfactory. He therefore postulated still a fourth gene which resulted in the appearance of both antigens and which he now calls R^1. (Genes will be printed in italics in this report, while antigens will appear in ordinary type.) These four genes were considered multiple alleles, and this explanation was logical at the time, since it was consistent with the known facts. At that time the postulated allelic genes were those which follow.

Anti-Rh blood typing serums are subject to the Biologics Control Law and must be licensed on recommendation of the National Institute of Health before being distributed in interstate commerce. The importance of appropriate and uniform designations for anti-Rh serums in labeling the test serums prompted the Surgeon General of the U. S. Public Health Service to seek the advice of experts in this field. The report and recommendations made by the Review Board are accepted by the Surgeon General. (Announcement of this conference appeared in *Science*, September 26, 1947, p. 288).

Gene	*Antigen(s) produced*
R^0	Rh_0
r'	rh′
R^1	Rh_0 and rh′
r	Neither antigen

Still later, in 1943, a third type of Rh antigen was discovered by Wiener (*13, 19, 27*), occurring in only 32% of the white population of New York. This antigen, originally named Rh″, and later renamed rh″ because of its relatively unimportant clinical status, was likewise found to be inherited on the basis of a dominant gene. Moreover, persons were found having both antigens Rh_0 and rh″, and such persons often transmitted these two antigens together to some of their offspring, just as individuals of type Rh_1 often transmitted both antigens Rh_0 and rh′ to the same offspring.

Wiener therefore logically added two new genes to the series of multiple alleles already postulated, namely, a gene r'', producing antigen rh″, and a gene R^2, producing both antigens Rh_0 and rh″. This made a series of 6 multiple alleles, of which any individual could carry two, and any gamete, one. At this point the 6 postulated allelic genes were as follows (*20*):

Gene	*Antigen(s) produced*
R^0	Rh_0
r'	rh′
r''	rh″
R^1	Rh_0 and rh′
R^2	Rh_0 and rh″
r	No antigen

Two new genes were then postulated by the British workers—r^y, producing antigens Rh′ and Rh″, and R^z, producing all three antigens (*11, 14*). Evidence for the existence of a gene giving the reactions postulated for r^y was offered by Stanca, Clark, and Snyder (*16*), and evidence for gene R^z was presented by Murray, Race, and Taylor (*11*).

As long as only the various Rh antigens were known, the hypothesis of multiple alleles and the Wiener nomenclature were unchallenged. About 1943, however, the picture began gradually to change. At that time Levine vigorously directed attention to his earlier discovery (*5, 6, 7*) of a new antiserum from an Rh-positive mother of an erythroblastotic infant, reacting against all Rh-negative and Rh_2 bloods but not on all Rh_1 bloods. The new antigen demonstrable by this serum was thus in some way antithetical to the Rh antigens, and Levine therefore named it Hr. Shortly thereafter Race and Taylor (*13*) reported a similar serum and named the antigen which it demonstrated St, from the first two letters of the name of the patient. The two antigens were subsequently found to be identical.

Further studies made it clear that antigen Hr was strictly antithetical to rh′, since it failed to react only with blood from those persons having two genes producing rh′. In other words, anti-Hr agglutinated the cells of everyone except persons of the genotypes $r'\ r'$, $R^1\ r'$, and $R^1\ R^1$. This antigen, then, was properly called Hr′; more recently, corresponding to the small letters used in rh′, it has been called hr′.

Prior to the discovery of the Hr factor, the Rh type of a person could be stated simply in terms of the Rh antigens and their shorthand designations. If it were desired to state not only the type but the genotype, that also could be done simply. Leaving out the very rare genes r^y and R^z, the blood types and genotypes could be expressed as follows:

Type	*Reaction with*			*Possible genotypes*
	Anti-Rh_0	*Anti-rh′*	*Anti-rh″*	
Rh_0	+	−	−	$R^0\ R^0$
				$R^0\ r$
Rh_1	+	+	−	$R^1\ R^1$
				$R^1\ r'$
				$R^1\ R^0$
				$R^1\ r$
				$R^0\ r'$
Rh_2	+	−	+	$R^2\ R^2$
				$R^2\ r''$
				$R^2\ R^0$
				$R^2\ r$
				$R^0\ r''$
$Rh_1\ Rh_2$	+	+	+	$R^1\ R^2$
				$R^1\ r''$
				$R^2\ r'$
rh′	−	+	−	$r'\ r'$
				$r'\ r$
rh″	−	−	+	$r''\ r''$
				$r''\ r$
rh′ rh″	−	+	+	$r'\ r''$
rh	−	−	−	$r\ r$

With the discovery of the hr′ antigen, however, it became difficult to describe the type in simple terms. Both an Rh and an Hr type had to be stated. Moreover, it was even more difficult to read the Hr into the genotype. Wiener maintained that the Hr antiserum merely defined an additional characteristic of the blood property and did not need to change in any way the gene designations.

In 1944 Race (*12*) published a suggestion of Fisher that, since hr′ was genetically related to rh′ as antigen M is to antigen N (a relationship originally pointed out by Levine), it was logical to suppose that Rh$_0$ and rh″ also had similar antithetical antigens which were capable of eventual demonstration. He suggested that each pair of antigens was similar to the familiar M-N pair and that, instead of all the Rh genes

being alleles of each other, the three pairs were separate and distinct, but closely linked genetically. He further suggested a new terminology to cover the new situation. The comparison of the old and the new terminology is as follows:

Known antigens	
Old	*New*
rh′	C
Rh_0	D
rh″	E
hr′	c
Predicted antigens	
Hr_0	d
hr″	e

Wiener (*28*) not only denied the linkage theory of Fisher and Race, but stated that his (Wiener's) views would preclude the existence of the two additional Hr factors (d and e) postulated by Fisher. Nevertheless, anti-hr″ (anti-e) serum was found by Mourant (*10*) and anti-Hr_0 (anti-d) by Diamond (*2*), thus bearing out Fisher's predictions. These facts turned the thoughts of many American workers toward the British nomenclature, and since 1945 the latter has consistently gained usage in the United States. The three pairs of antigens, each pair having the same intrapair relationship as M and N, are, on the Fisher terminology, C and c, D and d, E and e.

Every individual person must be either C, Cc, or c. No one, as far as is known, lacks both C and c. Likewise, everyone must be D, Dd, or d, and, in addition, E, Ee, or e. These relationships are identical with the well-known M-N relationships and are easily understood. It is not necessary to use C and c, D and d, E and e to achieve the result of designating three pairs of antithetical antigens. This could be done on the Wiener system by considering three pairs of antigens, rh′and hr′, Rh_0 and Hr_0, rh″ and hr″, and naming the Rh type in terms of one combination of each of the three pairs. Thus, each person would be typed as rh′, rh′hr′, or hr′; as Rh_0, Rh_0Hr_0, or Hr_0; and finally, also as rh″, rh″hr″, or hr″. Such designations would specify exactly the antigens carried.

Wiener, however, has insisted on a streamlined and elliptical nomenclature into which some of the antigens present must be read in the type designation, and into which the Hr antigens must always be read in the genotype designation. One of the commonest blood types, for example, is positive for Hr′. Genetically, the commonest situation would be for such a person to be heterozygous for Rh_0 and rh′. Such studies as have been made with anti-Hr_0 and anti-hr″ serums indicate that such persons are positive for Hr_0 and hr″. Let us compare the type designations and the genotype designations for such an individual on the two systems.

	Type	*Genotype*
Wiener	$Rh_1 + hr' + Hr_0 + hr''$	$R^1 r$
Fisher	CcDde	*CDe/cde*

In both the type and the genotype on the Fisher system, the antigens present are clearly specified. On the Wiener system the type specifies Rh_1, which must be translated into Rh′, and the genotype does not indicate directly any antigen. Antigens Rh_0, rh′, Hr_0, hr′, and hr″ must be read into the designation.

Another difference between the two systems of nomenclature involves the basic problem of the one-to-one correspondence between gene and antigen. On the Fisher system the one-to-one correspondence is upheld, a view which is rapidly being incorporated into genetic theory (*1*) and into the beliefs of immunologists (*30*). On the Wiener system certain genes result in the production of a single antigen, but others produce two or more antigens.

Throughout this report, wherever the Wiener system has been incorporated, the most recent of his suggested names have been used. This brings up another difficulty with the Wiener system. The rapid changes in his own nomenclature proposed by Wiener have been difficult to follow. Some of the changes were, of course, necessitated by new discoveries, but many of them were apparently made without clear reason. Some of the recent changes in the names of the Rh types are given in the above table.

	1941 (*3*)	1942 (*2*)	1943 (*21*)	1943 (*25*)	1944 (*29*)	1944 (*22*)	1946 (*23*)	1946 (*24*)
Rh pos.		Rh_2	Rh_1	Rh_2	Rh	Rh_0	rh_0	Rh_0
					Rh_2	Rh_2	Rh_2	Rh_2
		Rh_1	Rh_2	Rh_1	Rh_1	Rh_1	Rh_1	Rh_1
					Rh_1 Rh_2	Rh_1 Rh_2	Rh_1 Rh_2	Rh_1 Rh_2
Rh neg.		?	Rh_2	Rh′	Rh′	Rh′	Rh′	rh′
					Rh′ Rh″	Rh′ Rh″	Rh′ Rh″	rh′ rh″
		Rh neg.	Rh neg.	Rh neg.	Rh″	Rh″	Rh″	rh″
					Rh neg.	Rh neg.	rh	rh

During these years similar changes have been made in the names of the antiserums. Thus, the original anti-Rh′ is now anti-Rh_1, and anti-Rh″ has a new meaning; likewise, the original anti-Rh″ is now anti-Rh_2, and anti-Rh‴ has a new meaning (*22*). These rapid changes have not always been easy to follow.

In so far as the evidence for one or the other genetic theory is concerned, there is no genetic distinction between an hypothesis of multiple alleles and one of completely linked gene-pairs. If the three pairs of genes are completely linked, no distinction can probably ever be made on genetic grounds, and any distinction will have to be made on serological grounds such as the one-to-one correspondence of gene and antigen. On an hypothesis of complete linkage the various different genotypes would be considered to have arisen by mutation alone.

If the linkage hypothesis involves any partial (but very close) linkage, then crossing over may also be involved in the production of various genotypes. Under this hypothesis, a family in which one parent was completely Rh negative (*r r* or *cde/cde*) could have more than two kinds of children, whereas on the multiple-allele hypothesis only two kinds of children could result. Thus far, the family studies have not resulted in the discovery of any such family with more than two kinds of children. Such instances, however, would be expected with extreme rarity if linkage is very close.

Crossing over, if it occurs at all, however, would tend to bring the genes of the three pairs of factors into equilibrium. This fact might provide a statistical test for distinguishing between the hypotheses, but an adequate test of this sort has never been made. Wiener has claimed to have disproved the linkage hypothesis statistically (*21*), but the test was made on the comparison of two pairs of factors with three multiple alleles and actually proved only that neither hypothesis was adequate. Such a test has never been worked out for the comparison of three pairs of factors with 8 multiple alleles. At the present time the geneticists must admit that, on purely genetical grounds, either hypothesis is tenable.

To sum up, the points in favor of and against such system of nomenclature may be presented as follows:

In Favor of Wiener's Nomenclature

(1) It has priority, having been proposed by one of the discoverers.

(2) It is in use by many clinicians and research workers and is understood by them.

(3) It is used by nearly all the writers on the subject in the Western Hemisphere.

(4) No conclusive evidence has been presented against the theory on which it is based.

Against Wiener's Nomenclature

(1) It does not always specify the antigens present in the type name, and it almost never does so in the genotype name.

(2) It has changed rapidly from year to year.

(3) It is losing followers among the producers and users of serums.

(4) It involves complications, both typographical and genetic, of subscripts, superscripts, numbers, primes, and other symbols.

(5) It involves the somewhat doubtful assumption of multiple antigens produced by single genes.

In Favor of the Fisher-Race Nomenclature

(1) It always specifies in both type name and genotype name the individual antigens present.

(2) It is in wide usage in England, is gaining in usage in the Western Hemisphere, and hence may become the international standard.

(3) It is simple and direct, both typographically and genetically.

(4) It conforms to a one-to-one correspondence between gene and antigen.

Against the Fisher-Race Nomenclature

(1) It lacks priority.

(2) It is based on a genetic hypothesis which is purely theoretical and for which no clear proof exists —an hypothesis no more tenable on genetic grounds than Wiener's hypothesis.

Conclusions of the Board of Review

The Board, having carefully considered the above historical development of the two systems of nomenclature and having weighed the arguments in favor of, and opposed to, each system, is forced to the conclusion that for the present a compromise must be made, and both systems must be used on the container labels and package labels. Because the Wiener system has priority and is understood by everyone in the United States concerned with the production and use of anti-Rh serums, the Board recommends that the Wiener terminology appear first on the label, followed by the Fisher-Race terminology in parentheses. Typical labels would then appear somewhat as follows:

Anti-Rh Typing Serum (human)
Anti-Rh_0 (Anti-D)
Slide test
Lot No.
Manufacturer

Anti-Rh Typing Serum (human)
Anti-Rh_0' (Anti-C + D)
——— tube test
Lot No.
Manufacturer

Anti-Hr Typing Serum (human)
Anti-hr′ (Anti-c)
Capillary test
Lot No.
Manufacturer

Anti-Rh Typing Serum (human)
Anti-rh′ (Anti-C)
Slide test
Lot No.
Manufacturer

The package label and literature might contain, in addition to the above, the description of the test by means of which the serum is to be used.

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Science Education in Korea

Glenn A. Noble
California State Polytechnic College, San Luis Obispo, California

As CONSULTANT IN BIOLOGY FOR THE American Military Government in Korea, I recently had an opportunity to observe what the Japanese bequeathed that country in the way of ideas and equipment, what the Koreans did with that heritage, and what the Americans are doing to promote education in the sciences there.

Under Japanese control, advanced science education was available to favored Japanese and to only a very few lucky Koreans. When the Japanese were removed from the country in 1945, there was left such a paucity of Koreans trained in science that the country faced a crippling setback, not only in the practical applications of science but also in the more basic fields of research. Throughout southern Korea I heard the much-repeated statement: "We haven't the trained personnel."

Fortunately for the Koreans, the Japanese were not permitted to take equipment with them. As a result, there is a surprising amount of excellent apparatus in most middle schools and colleges. The assortment of this equipment is often peculiar, due not only to the fact that much of it was apparently purchased for special projects rather than for general student instruction, but also to the fact that no new apparatus could be secured during the war years. For example, in one small college which I visited there were several spectroscopes, a number of sextants, some large electric motors, and a few expensive galvanometers, but not enough of the simpler items to enable the students to conduct many of the routine physics experiments. Some schools were used to house American troops when we first moved into Korea. Discipline seemed to have been lacking, for much valuable equipment had been destroyed or stolen by our GIs. Several microscopes from the spectrometers mentioned above were taken. Enough material is available, however, to conduct most of the usual laboratory exercises. Surprisingly enough, almost all colleges and middle schools possess an adequate supply of microscopes, Japanese made and of good quality.

Supplies present a different picture. Chemicals especially are in much demand. In one college where the professor requested me to show him some modern

microtechnics there was no xylene, phenol, glycerol, alcohol above 90%, anesthetic, acetone, or formalin. A medical college class in parasitology had no hematoxylin or glycerol, and only one set of staining jars, most of which were badly broken. Another school had a plentiful supply of glassware with the exception of graduated cylinders, which were completely lacking. The only dissecting instruments in a biology laboratory class which I visited were pocket knives and old razor blades! There seemed to be sufficient clean microscopic slides and cover glasses, however.

Winter weather was the most discouraging factor we faced in carrying on laboratory work. There was no heat in any of the colleges visited. During the cold winter months there was no running water and no gas, and in most schools laboratory classes were not held. While demonstrating a staining method to a class in a medical school last January, the water with which I was rinsing a slide in a staining jar froze, covering the slide with ice. That particular demonstration could not be completed. The library in the same school was closed because of the intense cold. There was a considerable amount of ice on the floor—evidence of an earlier mopping.

Korean professors are, in the main, doing an excellent job, considering the circumstances under which they are working. Unfortunately, however, there is a tendency to let equipment and supplies deteriorate for lack of care. In several schools fine collections of marine shells, insects, parasitological specimens, and demonstration models were allowed to become broken, dried out, crushed, or destroyed through negligence. Most of these collections belonged to Japanese professors, and no Korean has taken an interest in them. Possibly the feeling of uncertainty toward the future of their country and so of their school is partly responsible.

The Department of Education, under the American Military Government, is trying to introduce much of the American system of education to the Koreans. The effort is only partially successful because of the tendency of the Koreans to cling to the system with which they are familiar and because of the small number and quality of some of the American members of the department. Under the Japanese system there was little or no laboratory work in many classes and a minimum of lecture demonstration. Nearly the entire day was filled with formal lectures which were almost memorized by the student. Equipment and supplies were used largely for professors' research. A storeroom or laboratory might have very little equipment, but each professor's private workroom possessed an abundance. Often only one examination was given in a course (the "final"), and sometimes passing the course depended in part on the political leaning of the student, or on his extracurricular activities. One Korean professor said to me: "I will pass those students because they did not take part in the strike last month."

The Education Department, following the lead of U. S. military authorities, encourages training of Koreans in the application of science to agriculture and to industry, but does not encourage basic research, without which all science progress is drastically limited. The men in charge have little interest or training in science. Last year the Department included consultants in chemistry, biology, and meteorology, but none in physics or in any other science. Furthermore, the new table of organization does not include consultants in any science except psychology. Obviously, Korea suffers from such limited vision in planning.

The need for textbooks and reference books is paramount. All over Korea one hears the plea: "Give us the latest books; we've seen nothing since 1941." Many students celebrated the country's liberation by burning Japanese textbooks—a destruction which was tragic because there are practically no texts in the Korean language for middle school and college students, and very few in English or German. The situation has not yet been relieved because of the monetary exchange condition which makes it impossible for Koreans to buy American books. The Department of Education is doing an excellent job in providing books in Korean for the lower grades, but it will be a long time before Korean books will be available to college students. Since most of these students can read some English, any recent books on any science subjects would be welcomed. If the readers of this article have such books which they would like to send to Korea, I will be glad to arrange shipment.

Obituary

Frank Rattray Lillie
1870-1947

Frank Rattray Lillie was born June 27, 1870, in Toronto, Ontario, Canada, and died in Billings Hospital on the campus of The University of Chicago on November 5, 1947, after a second cerebral hemorrhage following one 5 months earlier. There was thus terminated a brilliant career of notable value to science in general and to the biological sciences in particular. It can probably be said correctly that no man of the present century has contributed more to the over-all advancement of science, for he has served admirably as contributor, originator, organizer, and administrator.

Coming from a background of Scottish clergy on both sides of the family, and with some earlier contemplation of entering into the work of the church, Lillie attended preliminary schools in Toronto. Later, at the University of Toronto, he developed a great interest in science from contacts with Prof. Ramsay Wright and Dr. A. B. Macallum. Upon graduation from Toronto with the B.A. degree in 1891, he attended the summer session of the Marine Laboratory at Woods Hole, Massachusetts, and also entered Clark University for advanced studies under the general supervision of Prof. Charles Otis Whitman, whom he accompanied to The University of Chicago on its opening in 1892; in the then-new institution Lillie became a Fellow. He received his Ph.D. degree from The University of Chicago in 1894, publishing in the next year his thesis on "The Embryology of the Unionidae: A Study in Cell-Lineage," of which his first published paper in 1893 had been a preliminary account. From the publication of his thesis in 1895 up to the year 1945 (10 years after retirement), only 6 years passed without the appearance of a publication under his name; more than 90 have appeared.

Lillie's contributions center in a general way around 6 particular lines of major interest, in all of which *development* is a principal consideration; *embryology* was therefore his main province of scientific interest. His graduate students played a conspicuous role in the development of his work, for it was characteristic that he opened general problems for investigation, set up broad governing principles, and left to them the development of details.

His first investigations centered on studies of cell organization, differentiation, cell-lineage, cleavage, and regeneration; these interests stand out prominently in the literature from 1893 to 1909. As did other investigators of this period, he made considerable use of the centrifuge as an instrument of investigation.

His second field of interest pertained to the embryology of birds, and he is probably most widely known from the publication in 1908 of *The development of the chick,* one of the earliest textbooks in embryology. This text and a manual for laboratory study of chick development, which with one major revision has been in current usage from 1906 to the present time, provided the prospective student of biology or medicine with directions for study and descriptive details of chick development. The text embodied much of the studies on the early development of the bird by Whitman's students at The University of Chicago (Harper, Blount, Patterson) and of his own experimental investigations on the chick in 1903–04. The text, with only one slight revision, has served continuously for 35 years as the best account available on bird development. It has been used by countless numbers of students in colleges and universities of this and foreign countries; after such excellent and long service, it is now undergoing extensive revision by a younger embryologist.

Lillie's third principal line of interest in biology was that of a study of *fertilization.* Following logically from his earlier studies on organization and development of the egg of marine invertebrates, the problems of fertilization received a great deal of his attention during the summer sessions at Woods Hole from 1910 to 1921, when his tenth study on fertilization problems was published. In this field his graduate students became more evident, since many contributions to the general problem came from their studies directed by Lillie.

The fourth major problem was introduced in 1916–17 in his excellent contribution to the problem of the freemartin. The conditions described and analyzed pertain to the interference in sexual differentiation of the female embryo of the cow when twinned with a male, and it introduced the problem of the role of embryonic sex hormones in sexual differentiation. This investigation, which is considered by some to be his greatest, has stimulated a tremendous amount of research in the United States and in most foreign countries where embryological studies have been carried out; the literature on the subject during the past 5 years carries several able contributions from foreign

laboratories. His own students have contributed greatly to the general problem, and work is currently being pursued in attempts to provide final clarification of the thesis introduced by him 30 years earlier.

The fifth interest in research fields again followed logically from the preceding and centered around studies leading to the isolation of sex hormones and a study of their physiological role in the organism in connection with sex and reproduction. Since this period was an especially busy one in his career, his personal contributions were mainly those of planning, organizing, guidance of students, and synthesizing. His introductory chapter in the first edition of *Sex and internal secretions,* edited by Edgar Allen in 1932 (Williams and Wilkins, Baltimore), under the title *General biological introduction* admirably expresses his mastery of these problems and his fundamental interest in the field. His long membership on the Committee for Research in Problems of Sex, National Research Council, permitted him to exert a pronounced influence in the developments in this subject.

Following his retirement from The University of Chicago, the sixth and final major line of investigation centered around the physiology of development of the feather, to which he contributed a striking series of analyses, aided frequently by the application of hormonal substances. Here, as in all other of his major fields of scientific interests, Lillie's masterful touch was evident; and his last paper in the series, published in 1944 (with Hsi Wang), was an experimental study of induction in the physiological development of the feather; it reveals that embryology was still as much a central part of his interests as it was during his first investigation, published in 1893. His last scientific paper was his concise account on the "Feather," appearing in the 1947 *Encyclopaedia Britannica.*

Lillie's career as teacher and leader in science is impressive. After graduation he taught for short periods at the University of Michigan and Vassar College, but he returned to The University of Chicago in 1900 as assistant professor of zoology. He attained his professorship in 1906. He became the second chairman of the Department of Zoology (1910–31) and exercised his leadership in the gradual building of a strong department. He was named Andrew MacLeish distinguished service professor of embryology in 1931—one of the earliest of the university faculty to be so honored—and was called into university administrative service, during a reorganization period, to serve as dean of the Division of Biological Sciences from 1931 until his retirement in 1935 as emeritus professor. His retirement provided time for the continuance of his research interests on feather development, which he pursued actively until 1944. In 1926 Dr. and Mrs. Lillie presented to The University of Chicago the Whitman Laboratory of Experimental Zoology, to serve as a much-needed extension of research facilities for his department; it was named for his old teacher and first chairman of the department.

As an organizer and administrator, Lillie has played a leading role in the advancement of science throughout the present century. His greatest monument, perhaps, is the Marine Biological Laboratory at Woods Hole, Massachusetts, a unique experiment in a democratic organization, owned and operated by its members, who represent colleges and universities throughout the United States as well as many foreign institutions. When he first attended the Laboratory in 1891, it was a small and insecurely financed institution, operating upon an ideal and accommodating a very few interested biologists. Its first director, Prof. C. O. Whitman, had fostered as an ideal a democratic, friendly, cooperative organization of biologists owned and administered by its own membership. Its stormy, uncertain period of existence is well chronicled by Lillie's history of the laboratory, written in 1944 as one of the last of his contributions (*The Woods Hole Marine Biological Laboratory,* University of Chicago Press).

A half-century after his introduction to it, the Laboratory was the leading institution of marine biology in the world, possessed magnificent equipment, abundant space for large numbers of investigators from all lands, a leading reference library, and a large endowment; but it still fostered the same democratic spirit in its operations, its teaching program, and all its other functions of service to the advancement of science. To Frank R. Lillie more than to any other person must go the credit for this phenomenal accomplishment.

In the first year of Lillie's connection with the Laboratory, he was an investigator receiving instruction. Shortly, he became a member of the teaching staff in Zoology and very soon was placed in charge of Embryology. He served as assistant director from 1900 to 1908, becoming the second director upon the retirement of Whitman. During his directorship from 1908 to 1926, the Laboratory saw its greatest growth and consolidation, due very largely to his stimulating leadership and effective administration. From 1925 to 1942, he was president of the Corporation and the Board of Trustees and was president emeritus until his death. From 1891 until his illness confined him in June 1947, Dr. Lillie had never missed a summer session at the Laboratory.

This remarkable succession of many years of service in no measure expresses his real contribution to the

Laboratory. With his continuous interest in, and attention to, details and larger plans for the institution, Lillie epitomized the finest aspects of a sociological experiment. In the words of the then director, Dr. M. H. Jacobs, on the occasion of a celebration of Lillie's 60th birthday at the Laboratory on June 27, 1930:

> To Dr. Lillie more than anyone else, the laboratory owes its freedom from certain features of our American system of institutional management which are particularly irritating to scientists. To have preserved during the critical period of its enormous material expansion the atmosphere of freedom and informality which characterized its earlier days and to have kept alive the spirit of healthy cooperation which makes it possible for the group of scientists who compose the Corporation and the Board of Trustees to manage the affairs of their own institution without a cumbersome administrative machinery, without the services of efficiency experts, and with an almost unbelievable absence of friction of any sort, is a contribution of outstanding importance, not merely to the Marine Biological Laboratory but to Science and Education generally (Anniversary Supplement in Honor of Professor Frank R. Lillie, *The Collecting Net*, June 28, 1930).

Renowned as is that portion of his career so assiduously devoted to the developments of the Marine Biological Laboratory, Lillie's services and influence reached out at the same time to additional spheres of planning and development. From 1935 to 1939 he was president of the National Academy of Sciences and in 1935–36 was chairman of the National Research Council. This combination of duties brought his organizing genius to bear upon the problem of coordination of the activities of these two national organizations. He is the only man ever to have held the leadership in the two organizations at the same time. In addition, he was appointed chairman of a committee of the National Academy of Sciences to study the problem of organization, location, financing, and construction of an Institute of Oceanography. The efforts of this committee can now be appreciated when one becomes acquainted with the fine Oceanographic Institute, also located in Woods Hole, immediately next to the Marine Biological Laboratory. Lillie served as president of the Oceanographic Institute from 1930 to 1939.

Honor has been bestowed upon him by membership in many societies and organizations in this country and abroad. He was managing editor of *Biological Bulletin* from 1902 to 1926 and was a member of the editorial boards of four or more journals as death overtook him. He has received honorary degrees from the University of Toronto and from Yale, Harvard, and Johns Hopkins Universities.

His last physical remains were sent to Woods Hole for interment in the churchyard of the Episcopal church, overlooking Little Harbor. Here he joins such other famous biologists as C. O. Whitman, Jacques Loeb, E. B. Wilson, Gary N. Calkins, C. E. McClung, and L. L. Woodruff, with whom he had worked for so many years. It is a fitting tribute to his love, devotion, and labors on behalf of an institutional ideal in science that so firmly bears the imprint of his genius, and so thoroughly casts its influence over the world, that he should thus be laid at rest nearby.

CARL R. MOORE

The University of Chicago

NEWS and Notes

The $1000 Prize for "a notable contribution to science," established in 1923 by a generous friend of the AAAS who desires to remain anonymous and awarded at annual meetings of the Association, was presented in Chicago to 30-year-old Harrison S. Brown, assistant professor of chemistry at the Institute for Nuclear Studies, The University of Chicago. Dr. Brown's paper, "Elements in Meteorites and the Earth's Origin," was selected from over 2,000 papers by a Prize Committee consisting of Dean Fernandus Payne (zoology), Indiana University, chairman; A. J. Dempster (physics), The University of Chicago; Malcolm Dole (chemistry), Northwestern University; and William R. Taylor (botany), University of Michigan. This week's cover photo shows F. R. Moulton, administrative secretary of the Association, presenting the prize to Dr. Brown in the presence of Drs. Dempster and Dole.

To be eligible for consideration for the $1,000 Prize, a paper need not be presented by a member of the Association, but it must not be an official address or an invited paper. The donor has expressed the wish that particular consideration be given to younger scientists and that the award be made to a single person rather than divided among several.

About People

Wallace Reed Brode, formerly professor of chemistry, Ohio State University, and widely known for his work in spectroscopy, is the new associate director of the National Bureau of Standards. Dr. Brode succeeds Hugh L. Dryden, who was recently appointed director of aeronautical research, National Advisory Committee for Aeronautics. Dr. Brode will act as liaison between the Bureau and the Department of National Defense and will also coordinate Bureau research done for other Federal Departments.

Samuel W. Dudley, dean of the Yale School of Engineering and director of the University's Division of Engineering, will retire at the end of the current academic year. **Walter J. Wohlenberg,** Sterling professor of mechanical engineering and chairman of the Department, will succeed Dean Dudley.

Hans F. Mayer, former director of the Berlin laboratory of the Siemens & Halske electrical firm, has been appointed professor of electrical engineering at Cornell University. Dr. Mayer is internationally known in the engineering field through numerous technical publications.

Alfred M. Lee, executive director and treasurer of the Institute for Propaganda Analysis and currently on leave of absence as chairman of Wayne University's Sociology Department, is engaged in a research project on public opinion and opinion manipulation under a grant from the Marshall Field Foundation. The results of his research will be published in book form late this year.

Grants and Awards

A grant of $6,000 has been made to the Biochemical Institute of the University of Texas by the Research Council on Problems of Alcohol to enable the staff to undertake fundamental research on individual patterns of metabolism in order to determine the possible relationship of body processes to susceptibility to alcoholism. All types of people will be subjects for the study, including members of Alcoholics Anonymous, identical twins, and men and women of Irish and Jewish ancestry who generally have very different patterns in drinking. Anton J. Carlson, president of the Council, explained that this research program will fill a definite gap in alcohol studies, in determining whether there are "any unique physiological characteristics in various tissues of the body which make some individuals more prone to problem drinking than others." Earlier in the year a grant of $30,000 a year for 5 years was made to Cornell University Medical College-New York Hospital for similar research.

A new center for the study of methods of collecting, organizing, and communicating knowledge will be established at the Massachusetts Institute of Technology under a $100,000 grant from the Carnegie Corporation of New York. Facilities will be provided for research and experimentation on aspects of printing, documentary reproduction, visual education, sound recording, and mechanical selection systems and for the training of technicians, librarians, and those working in allied fields.

The program, both national and international in scope, will profit by investigations already in progress at MIT. Microfilm and reading machines are already in use, and basic research in sound recording, applied acoustics, phonetics, and instruction through audio processes is under way in the new acoustics laboratory, the Departments of Modern Languages, English and History, and others. Mechanical selection is being studied in the Department of Electrical Engineering, and its application to the chemical literature being investigated by the Department of Chemistry under the sponsorship of the American Chemical Society.

Colleges and Universities

In the Department of Agronomy, State College of Washington, Pullman, several additions and changes have been made in both the teaching and research staffs in the past year.

Additions to personnel who serve on the staff of both the Agricultural Experiment Stations and the College of Agriculture include the appointments of **L. P. V. Johnson,** formerly assistant professor of agronomy, University of Florida, as assistant professor of agronomy and assistant geneticist in cereal investigations; **W. Keith Ken-**

nedy, Cornell University, as assistant professor of agronomy and assistant agronomist in forage investigations; **J. Roger McHenry,** formerly assistant professor of agronomy, University of Nebraska, as assistant professor of soils and assistant soil scientist to serve as soil physicist; **Lowell W. Rasmussen,** Iowa State College, as assistant professor of agronomy and assistant agronomist in weed research; and **John Unrau,** University of Saskatchewan, as instructor in farm crops and junior agronomist.

Appointments to the staff of the Agricultural Experiment Stations include **H. E. Dregne,** formerly assistant professor of agronomy, University of Idaho, as assistant soil scientist in charge of developing a soil testing program in the State of Washington; **Verne Comstock,** Washington State College, as assistant agronomist with the Division of Forage Crops and Diseases, USDA; **John J. Sturm,** Montana State College, as assistant agronomist and superintendent of the Adams Branch Experiment Station, Lind, Washington; **V. F. Bruns,** Hayes Field Station, Kansas, as assistant agronomist with the Division of Cereal Crops and Diseases, USDA, at the Irrigation Branch Experiment Station, Prosser, Washington; **Thomas L. Jackson,** Washington State College, as junior agronomist in charge of outlying field experiments; **Mrs. L. O. Cade,** Washington State College, as draftsman for soil survey; and **C. Grant Richins,** Brigham Young University, as assistant in soil survey.

R. A. McCreery, University of Georgia, has been appointed instructor in soils in the College of Agriculture.

Changes include the transfer of H. D. Jacquot from the position of superintendent and associate agronomist at the Adams Branch Experiment Station to the Agricultural Experiment Station at Pullman as associate agronomist, and the promotion of C. D. Moodie, instructor in soils, to assistant professor of soils.

The University of Cincinnati Observatory has published a 56-page star catalogue which lists 2,300 stars and supplements the first catalogue put out by the Observatory 25 years ago, which lists 4,683 stars. Both catalogues record such data as precessions, secular variations, proper motions, and final positions for the nearly 7,000 stars. The publication of this final catalogue marks the completion of the Observatory's program of determining the proper motion of stars with a meridian circle which was begun 40 years ago by the late Elliott S. Smith of the Observatory staff, who was aided by the late Jermain G. Porter, then director of the Observatory, and Everett I. Yowell, another former director and now professor emeritus of astronomy. The most recent of the data were prepared for publication by Paul Herget, present director of the Observatory. The work was completed in 1940, but publication was delayed until now because of the war.

Meetings and Lectures

The 12th Annual Theobald Smith Memorial Lecture of the New York Society of Tropical Medicine will be given January 16 at 8:30 P.M. in the Auditorium of Cornell University Medical College, 1300 York Avenue, New York City. Cornelius B. Philip, principal medical entomologist, Rocky Mountain Laboratory, U. S. Public Health Service, will speak on "Scrub Typhus (Tsutsugamushi Disease) in World War II." All who are interested are invited to attend.

The First International Congress of Physiology and Pathology of Animal Reproduction and of Artificial Insemination has been scheduled for June 23–30, 1948, in Milan, Italy, to enable participants to take part also in the International Congress of Genetics, July 7–14, in Stockholm, and the International Congress of Zoology, July 21–27, in Paris. A preliminary conference will be held June 21 under the auspices of UNESCO, at which a limited number of Italian and foreign specialists will discuss "Interacting Substances of Eggs and Sperm and Parthenogenesis." Full sessions of the Congress will cover topics of general interest in the fields of biological problems of animal reproduction, breeding problems of animal reproduction, pathological problems of animal reproduction, methodological and practical problems of artificial insemination of animals, and legislative and organizational problems of artificial insemination and of animal reproduction. Those desiring to present papers at the Congress should submit them before March 31. Both papers and inquiries for further information should be sent to the Secretary General of the Congress, Prof. T. Bonadonna, Via Bronzetti 17, Milan, Italy. The Congress is open to all who are interested at a subscription fee of $8 for active members, and $4 for associate members. An International Exhibition and livestock shows are also being organized in connection with the Congress.

The American Institute of Electrical Engineers will hold its winter general meeting in Pittsburgh, Pennsylvania, January 26–30, with headquarters at the William Penn Hotel. The program includes about 50 different sessions on many varied topics, and a general session, Wednesday morning, at which the Edison Medal will be presented to Joseph Slepian, associate director of research, Research Laboratories, Westinghouse Electric Corporation, and an address on "Solar Radiation and Its Effect Upon Power Transmission and Radio Communication" will be given by Jack T. Wilson, physicist, Allis-Chalmers Manufacturing Company. Fourteen inspection trips have also been arranged to various industries and institutions. The Eta Kappa Nu recognition dinner will be held Monday evening in the Urban Room, with W. J. Lyman, of Duquesne Light Company, as chairman. Registration should be made in advance to B. M. Jones, Chairman, Registration Committee, Winter General Meeting, Duquesne Light Company, 435 Sixth Avenue, Pittsburgh 19, Pennsylvania.

Elections

The Institute of Medicine of Chicago has announced the election of the following new officers for 1948: William F. Petersen, chairman of the Board of Governors; Henry T. Ricketts, vice-chairman of the Board; Dallas B. Phemister, president; Fred C. Koch, vice-president; George H.

Coleman, secretary; and Grant H. Laing, treasurer.

At the annual meeting of the Institute on December 2, citizen fellowship was conferred on Martin H. Kennelly, Mayor of the City of Chicago, and on Chauncey B. Borland, trustee of St. Luke's Hospital.

Harry M. Gehman, professor of mathematics, and chairman, Department of Mathematics, University of Buffalo, has been elected secretary-treasurer of the Mathematical Association of America for a 5-year term, succeeding Walter B. Carver, professor of mathematics, Cornell University.

The Conference of Professors of Preventive Medicine, at its recent annual meeting, elected as its president Henry E. Meleney, Hermann Biggs professor of preventive medicine, New York University College of Medicine. A mimeographed directory of persons engaged in teaching preventive medicine and public health in the 88 medical schools in the United States and Canada was issued at the meeting. Copies of this directory may be obtained by writing to Thomas D. Dublin, Secretary, 248 Baltic Street, Brooklyn 2, New York.

Deaths

Winfred E. Allen, 73, formerly a biologist at the Scripps Institution of Oceanography, La Jolla, California, died September 17 at Santa Paula, California.

Maurice A. Blake, 65, head of the Department of Horticulture, College of Agriculture, Rutgers University, died at New Brunswick, New Jersey, December 14 of a heart attack. Prof. Blake, during the course of his work, had developed more than 30 varieties of peaches.

Of interest not only to systematic zoologists but to specialists in tropical diseases is an announcement made by Francis Hemming, secretary to the International Commission on Zoological Nomenclature (On the status of the generic name *Schistosoma* Weinland, 1858 (Class Trematoda, Order Digenea) in relation to Opinion 77. *Bull. zool. Nomenclature,* 1947, **1,** Pt. 9, 195–196). In 1922, in Opinion 77, the name *Schistosoma* was placed by the Commission on the Official List of Generic Names. As Dr. Hemming points out, when such action is taken, that name and no other is the correct name for the genus in question. It was at that time believed that the name *Bilharzia* was first published by Cobbold in 1859; subsequently it has come to light that the name *Bilharzia* (misspelled *Billharzia*) was proposed by Meckel von Hemsbach in 1856 as a generic name for the trematode described by Bilharz as *Distomum haematobium.* Two alternative steps are now open to the Commission; these have been stated by Dr. Hemming as follows:

"(a) The International Commission could delete the invalid name *Schistosoma* Weinland, 1858, from the *Official List* and could insert in its place the valid name *Bilharzia* Meckel von Hemsbach, 1856, or

"(b) The International Commission, if satisfied that the strict application of the rules as applied to the present case would clearly result in greater confusion than uniformity, could use their plenary powers (i) to suppress the name *Bilharzia* Meckel von Hemsbach, 1856 and (ii) to validate the name *Schistosoma* Weinland, 1858, thereby giving retrospectively valid effect to the entry regarding the last-mentioned name in Opinion 77.

"Specialists are, therefore, invited to inform the International Commission which, in their view, of the alternative courses indicated above is the one to be preferred."

Communications should be sent to Dr. Hemming at 83 Fellows Road (Garden Flat), London, N. W. 3, England.

The name *Schistosoma* has been widely used for species of importance in human and veterinary medicine. The disease produced in man has received considerable attention in the Western Hemisphere in recent years and here, as in Asia, has been termed schistosomiasis; the parasites are widely known as *Schistosoma mansoni* and *Schistosoma japonicum.* It is hoped that persons concerned with these investigations will express their views to the Commission. (ELOISE B. CRAM, *National Institute of Health, Bethesda, Maryland.*)

A Department of Research in Physical Chemistry has recently been established at Mellon Institute, according to Director Edward R. Weidlein. Under the headship of John R. Bowman, physical chemist and chemical engineer, who since 1935 has been at the Institute on the multiple fellowship of the Gulf Research and Development Company, the Department will conduct fundamental investigations in its domain for professional and public benefit and will also act in an advisory capacity to other Institute members.

The Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, reports that common names for two insecticidal chemicals have been filed in the Trade-Mark Division of the Patent Office for recordation. After consultation with representatives of several scientific associations, the Federal Government, and industry, "methoxychlor" has been selected as the common name for 2,2-bis(p-methoxyphenyl)1,1,1-trichloroethane, the methoxy analog of DDT, and "parathion," for 0,0-diethyl 0-p-nitrophenyl thiophosphate, an ester of thiophosphoric acid.

Make Plans for—

American Academy of Orthopaedic Surgeons, January 24–29, Chicago, Illinois.

American Institute of Electrical Engineers, Winter General Meeting, January 26–30, Pittsburgh, Pennsylvania.

American Council of Learned Societies, January 29–30, Westchester Country Club, Rye, New York.

American Society of Heating and Ventilating Engineers, February 2–5, New York City.

American Philosophical Society, February 13–14, 104 South 5th Street, Philadelphia, Pennsylvania.

TECHNICAL PAPERS

Levo-Arterenol

M. L. TAINTER, B. F. TULLAR, and F. P. LUDUENA

Sterling-Winthrop Research Institute, Rensselaer, New York

In 1910 Barger and Dale (*3*) speculated that the sympathetic effector substance might not be epinephrine but rather a catechol with a primary amine side chain. Efforts to demonstrate the existence of such a hormone and to identify it have continued uninterruptedly ever since. In recent years several investigators (*1, 2, 4, 5, 6, 8*) have conjectured that 3,4-dihydroxyphenylethanolamine (arterenol, norepinephrine, noradrenalin) might be the substance in question (sympathin E), although only indirect evidence has been adduced in support of this hypothesis. If the true hormone is arterenol, it might be supposed that it would be the *l*-isomer, rather than the *d*-isomer or the racemic mixture since *l*-isomers are generally more active.

Thus, the desirability of obtaining and studying *l*-arterenol has been appreciated for some time (*4, 5*). However, despite numerous efforts on the part of many investigators, arterenol has hitherto resisted resolution. Although Greer, *et al.* (*5*) indicated in 1938 that they were attempting the resolution, no report of success on their part has ever appeared. In our laboratory the problem has been under investigation for many years. Numerous trials at direct resolution by means of optically active acids failed, as did efforts at the resolution of regenerable derivatives of arterenol.

The purpose of this paper is to announce the successful preparation of *l*-arterenol by one of us (Tullar) and to present a brief description of its physical and physiological characteristics. Complete details will soon be published by us individually in appropriate journals.

The successful resolution of arterenol has now been accomplished by taking advantage of the fact that only the *l*-isomer forms a hydrated diastereoisomer with *d*-tartaric acid. From an aqueous solution of equimolar amounts of racemic arterenol and *d*-tartaric acid, the monohydrate of *l*-arterenol *d*-bitartrate crystallizes. The crude *d*-arterenol *d*-bitartrate from the mother liquor is purified by crystallization from 90% aqueous methanol. The optically active forms of arterenol are then readily obtained from these salts by treatment in aqueous solution with ammonium hydroxide.

Levo-arterenol hydrochloride is a white crystalline solid which is freely soluble in water. Solutions slowly oxidize under the influence of light and oxygen in a manner comparable to epinephrine hydrochloride. The melting points and optical rotations are given in Table 1.

As has been postulated from the activity of the *dl*-form (*7*), the *l*-isomer is more active in raising blood pressure than the *dl*- or *d*-form. In dogs under phenobarbital anesthesia this activity was found to be 164 ± 10% of that of *l*-epinephrine. This would give to *l*-epinephrine a dosage ratio of 0.61 for equal effect, a figure in excellent agreement with that of 1.2 for the racemic mixture, reported previously (*2, 7*). Dextro-arterenol has only 3–4% of the pressor activity of the levo, a ratio similar to that of the epinephrine isomers. The general shape of the blood pressure curve of *l*-arterenol is like that of *l*-epinephrine, except that the secondary depressor phase is uncommon. The relative absence of stimulation of vasodilators is demonstrated also by the injection of Compound 933F (piperidinomethylbenzodioxan). At a time when *l*-epinephrine is reversed by this drug to a pure vasodilator action, *l*-arterenol still retains a small part of its pressor power and shows no reversal. In this respect, *d*-arterenol acts similarly to the *l*- in equivalent doses. Cocaine sensitizes the pressor response to *l*-arterenol to a considerably greater degree than to *l*-epinephrine.

TABLE 1

	Physical Properties	
	M.p. (corrected) °C	$D^{25-5°}$
l-Arterenol	216.5–218	−37.3
d-Arterenol	215 –217	+37.4
l-Arterenol hydrochloride	146 –147	−39
d-Arterenol hydrochloride	146.8–147.4	+39

TABLE 2

ACUTE TOXICITY OF INTRAVENOUSLY INJECTED ARTERENOL AND EPINEPHRINE FOR MICE AT THE END OF 24 HOURS

Compound (as base)	LD_{50} in group cages (mg/K)	LD_{50} in individual cages (mg/K)
l-Epinephrine	2.4 ± 0.2	3.5 ± 0.2
l-Arterenol	6.1 ± 2.0	20.5
d-Arterenol	70.7 ± 42.8	> 66

Excised strips of rabbit and guinea pig ileum are relaxed by *l*-arterenol to about the same degree as by *l*-epinephrine. However, on the nonpregnant rat uterus the *l*-arterenol is a relatively weak inhibitor, since it takes 30 times the concentration to reproduce the relaxation of the stimulated organ produced by *l*-epinephrine. These results indicate that *l*-arterenol can produce inhibitory effects in at least some organs, but that its spectrum of action differs from that of epinephrine.

The acute intravenous toxicity for rapid injection in mice is summarized in Table 2.[1] It was found that the

[1] The authors are indebted to J. O. Hoppe for the toxicity determinations.

toxicity of the *l*-arterenol is reduced when the animals are kept in individual cages, as shown in the last column of the table.

The arterenol toxicity curves are quite flat, as is indicated by the relatively large standard errors. These figures indicate that for equivalent pressor doses *l*-arterenol has a safety ratio (toxicity to pressor activity) which is approximately 4 times that of *l*-epinephrine. This is in agreement with the earlier results (*7*) on the racemic mixture.

Now that *l*-arterenol has been obtained and can be made available for physiological experimentation, it is expected that complete elucidation of its role in the mediation of sympathetic functions and application to therapeutics will follow promptly.

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Nitrogen Mustards in Fowl Leucosis[1]

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The recent reviews by Bodansky (*1*) and by Gilman and Philips (*3*) indicate that nitrogen and sulfur mustards elicit a variety of systemic pharmacological actions, chief of which is their ability, in some unexplained manner, to produce death of cells. The generalization is made that cellular susceptibility is related to proliferative activity. The action of the mustards on the blood-forming organs as reflected in the peripheral blood of both experimental animals and man results in a lymphocytopenia, granulocytopenia, thrombocytopenia, and moderate anemia. Because of the marked effects of the mustards on lymphoid tissue, coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards, therapeutic use of these compounds in the treatment of neoplasms of lymphoid tissue in fowls was undertaken. The use of nitrogen mustards in such diseases as Hodgkin's disease, lymphosarcoma, and leucemia in man was sufficiently encouraging to warrant studies with similar diseases of animals (*4*, *6*).

Leucosis of fowls is a disease somewhat similar to leucemia of mammals. In fowls the disease is transmissible, and the causative agent is recognized as a filtrable virus. Several forms of the disease occur, depending upon the type of proliferating cells in predominance and upon the tissues involved. The various forms have been designated as lymphomatosis, which may be neural, visceral, ocular, or osteopetrotic and may be leucemic, subleucemic, or aleucemic; and leucosis, which may be erythroblastic or granuloblastic (*9*).

The birds used in these experiments were purchased as day-old chicks from a nearby hatchery and were infected artificially when they were from 1 to 2 weeks of age.

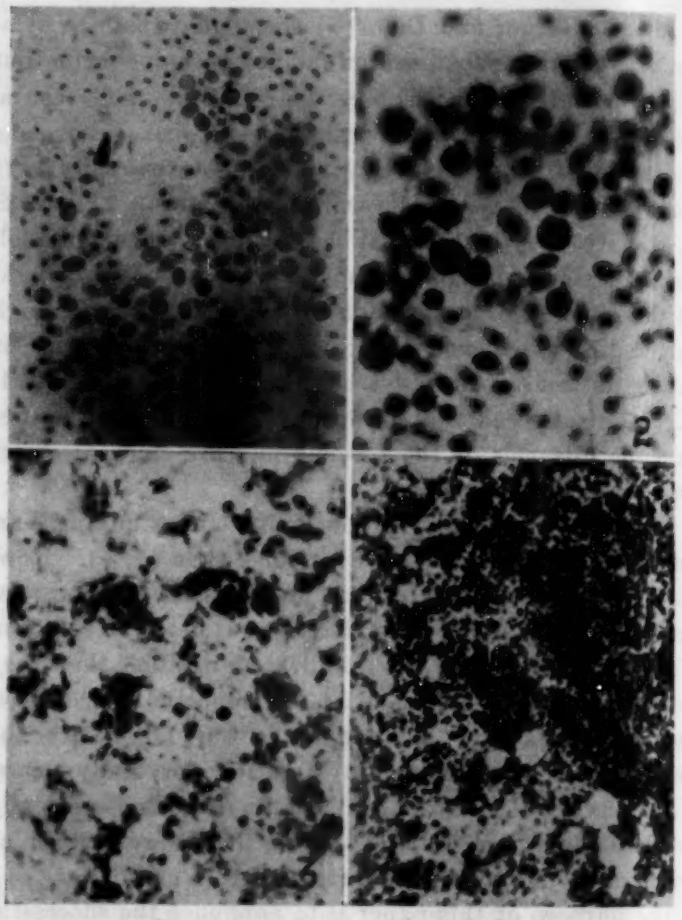

Fig. 1. (1) Photomicrograph of blood smear from chicken with hemocytoblastic leucosis, stained with Wright's stain (×368). (2) Same as (1) at higher magnification (×750). A marked reduction in numbers of these large immature cells was noticeable as early as 24 hrs following treatment with the nitrogen mustards. Note one cell in mitosis. (3) Photomicrograph of femoral marrow from a chicken 4 days after receiving a toxic dose of mustard (×368). Note depletion of lymphoid cells. (4) Photomicrograph of femoral marrow from a normal chicken of the same group and of the same age. Note hyperplasia in contrast to (3).

About equal numbers of the Barred Plymouth Rock and New Hampshire Red breeds were used. The Beltsville strain "A" leucosis virus was used throughout (*5*). When week-old chicks were injected intravenously or intraperitoneally with blood containing this strain of virus, they usually developed an acute form of erythrogranuloblastic leucosis in from 4 to 6 weeks. The injected birds that did not develop an acute form usually later developed either a chronic visceral form characterized by great enlargement of the liver, spleen, and other visceral organs or the nerve form characterized by cellular infiltration of nerves, and paralysis (*10*). The

[1] The nitrogen mustards were obtained through the courtesy of the Medical Division of the Army Chemical Center.

acutely affected birds usually developed an overwhelming preponderance of immature cells in the peripheral blood, referred to by Jordan (*8*) as hemocytoblasts, and were in effect cases of hemocytoblastic leucosis (Fig. 1, 1 and 2). Of these that were treated with the mustard compounds there were 15 that had acute hemocytoblastic leucosis and 13 that had neural lymphomatosis. Four had visceral lymphomatosis characterized by enormous enlargement of the liver as determined by rectal palpation. In this form any of the visceral organs may be diffusely infiltrated with lymphoid cells, or there may be multiple tumor masses made up chiefly of these cells (*7*).

One was a case of ocular lymphomatosis in which the iris of the affected eye was densely infiltrated with lymphocyte-like cells (*10*).

The preliminary work consisted of a determination of the approximate optimal and safe dose of the two mustard derivatives used, namely, methyl-*bis*(β-chloroethyl)-amine (HN_2), and *tris*(β-chloroethyl)amine (HN_3). This was accomplished by injecting normal chickens weighing approximately 0.5 kg each with varying amounts of the mustards. Ten such birds were injected intravenously (*vena ulnaris*) with a gradually increased dose of the HN_2 compound per bird, ranging from 0.5 to 10 mg/kg body weight, each dose being dissolved in 2 ml of sterile physiological sodium chloride solution immediately before administration. In a similar manner, 10 comparable birds were injected with the HN_3 compound. It was found that, when from 3 to 5 mg/kg of HN_2 was given, there was drooling of fluids from the mouth, some diarrhea that persisted for about 24 hrs, and evidence of leucopenia without lethal results. The HN_3 compound was found to be about twice as toxic as the HN_2. In general, the symptoms produced by the two compounds were similar. There seemed to be considerable individual variation in the reaction of birds to both compounds. From these experiments with each compound on 10 normal birds, weighing about 0.5 kg each, it appears that the optimal dose of HN_2 is approximately 2 mg/kg, and of HN_3, approximately 1 mg/kg. At autopsy of the birds that died 24–72 hrs after treatment with either of these compounds, the spleen was found to be considerably shrunken and the femoral marrow was of a yellowish color, denoting depletion of hemopoietic cells. Suitable portions of heart, liver, spleen, pancreas, duodenum, sciatic nerve, femoral marrow, and thymus from these birds were fixed in Helly's fluid, sectioned at 5 μ, and stained with Delafield's hematoxylin and azur-eosin. Microscopic examination of these revealed marked atrophy of lymphoid tissue in spleen, thymus, duodenum, and femoral marrow. The most pronounced microscopic lesions after a lethal dose were observed in the marrow, spleen, and intestines. In the marrow there was a marked decrease in numbers and in mitotic activity of hemopoietic cells. This depletion of the marrow progressed until the sinusoids contained only a few mature cells, and if the bird lived for a few days after the treatment, there was almost complete aplasia (Fig. 1, 3 and 4). A similar depletion of lymphoid cells occurred in the spleen. The intestinal lesions consisted chiefly of vacuolization of epithelial cells and atrophy of adjacent lymphoid tissue.

The birds with hemocytoblastic leucosis contained enormous numbers of immature cells (hemocytoblasts) in their peripheral blood when treatment was started. In the cases that responded to treatment there was a marked reduction in these cells 24 hrs after treatment. In two such leucotic birds that were killed one week after receiving the mustards, the spleen and liver were practically of normal size. These organs are invariably enlarged in this form of leucosis. Likewise, in two birds with marked enlargement of the liver as determined by rectal palpation, there was practically complete reduction to normal size of this organ two weeks following one treatment with the HN_2 compound. Six birds with neurolymphomatosis responded to treatment and made a complete clinical recovery. Most of the birds that recovered, especially when more than one treatment was necessary, developed a transient leucopenia and slight anemia that was noticeable about two weeks after treatment.

Fourteen birds infected artificially with strain "A" leucosis were treated with HN_3 and 19 similarly infected birds were treated with HN_2. Two of these, in the early stages of the hemocytoblastic form when treated with HN_3, made clinical recoveries lasting from 3 to 6 months following the last treatment. Three with hemocytoblastic leucosis, 6 with neurolymphomatosis, and 2 with visceral lymphomatosis when treated with HN_2 have made complete clinical recoveries. In addition, 7 spontaneous cases were treated. One of these was a case of the visceral form treated with HN_3 without response. Three with neural and 3 with the visceral form were treated with HN_2. One of each showed improvement but recurred. One of the visceral cases made a complete recovery lasting 8 months. The others did not respond.

The results, while not highly impressive, appear to indicate that, if these compounds are given in the early stages of the disease, the results are better and more apt to be of a permanent nature. In advanced cases the effects were only temporary, and a recurrence of the disease usually resulted in death of the bird. There may have been several factors that played a part in the results obtained. Smaller doses repeated more frequently, as well as the use of larger quantities of saline to dilute these mustards prior to injection, should be tried. The effect, if any, upon the blood vessels should be studied to learn if any permanent injury occurs. It is interesting to note, however, that in 9 birds out of 33, clinical recovery resulted after one treatment.

In some instances, especially when repeated treatments seemed necessary, intravenous injections were difficult to accomplish. This was due to the irritation set up from some of the mustard escaping into the subcutaneous tissues. Because of the marked irritation and subsequent formation of scar tissue around the vein, it is important to exercise care in making the injections to avoid damage to the sites for future intravenous therapy.

The work related herein indicates that the two nitrogen mustards used have a profound action upon the immature

cells spoken of as hemocytoblasts in a highly fatal disease of fowls. In many instances a retardation of mitotic activity both in the marrow and in the peripheral blood was demonstrable 24 hrs after treatment. Some evidence to indicate that these mustards have a lethal effect upon the causative virus in addition to causing death of the proliferating cells was indicated by the failure of blood drawn from treated birds to transmit the disease.

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In Vitro Studies of Caries of the Enamel in the Syrian Hamster

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In previous pathological studies of enamel caries in the human (*1*, *2*) and hamster (*4*) it was observed that two morphological types of microorganisms were constantly associated with the microscopic plaque and the early enamel lesion. Thread forms predominate in the more superficial areas of the plaque, whereas spheroidal forms were always present in the affected enamel beneath the plaque. As a follow-up of this observation, it seemed advisable to attempt to isolate and culture these organisms.

Scrapings were taken from the plaque overlying the early carious area, in which the first evidence of enamel caries is the appearance of a brown-stained spot in an apparently intact enamel surface. The scrapings were cultured, and a growth of filamentous forms was obtained which resembled those found predominating in the plaque of the earlier histological sections. These organisms developed on blood agar after incubation at 37° C for 4–5 days. An atmosphere of about 10% carbon dioxide seemed to be favorable for primary isolation. Subsequently the organisms will grow on a variety of media. Fermentation of the carbohydrates tested in the growth of the organisms was slow with the different strains tested. Gelatin was not liquefied, but the colonies developed a dark brown pigment in 1–2 weeks in this medium.

These organisms are similar to the actinomycetes, a group which has been called simple molds or pleomorphic bacteria. They are easily identified with some of the *Leptothrix* and *Cladothrix* described in the earlier literature under terms no longer used. Except for their more aerobic habits and the ease with which they are cultivated, they correspond closely with some strains isolated by several workers from normal mouths and throats, from carious detritus, gingivitis, and cervicofacial actinomycosis, and classified as *Actinomyces bovis* or *A. israeli*.

A high degree of pleomorphism is characteristic of these isolated filamentous organisms. Various small forms resembling diphtheroids, short bacilli, and irregular cocci, as well, were frequently observed to be associated with the filamentous cells in a single colony. After repeated subculture, some of these associated forms almost completely replaced the filaments. The change in the appearance of the filamentous types to other morphological forms may be accompanied by a change in the appearance of the colony, but this is not always the case. The filamentous colony is rough, whereas when transition to other forms takes place, the colony may have a smooth, glazed appearance. Neither the age of the culture nor the type of media has thus far been shown to be associated with the change in the morphological appearance of the cells. While the various cell types of the colonies most likely represent a single highly pleomorphic species, the possibility of a symbiotic relationship between two or more species which are difficult to separate in culture could not, at this point, be entirely ruled out.

Isolated filamentous cells growing on laked blood agar were selected for study and their multiplication was recorded with photomicrographs at definite intervals of time (Fig. 1). These observations were made at 2-hr

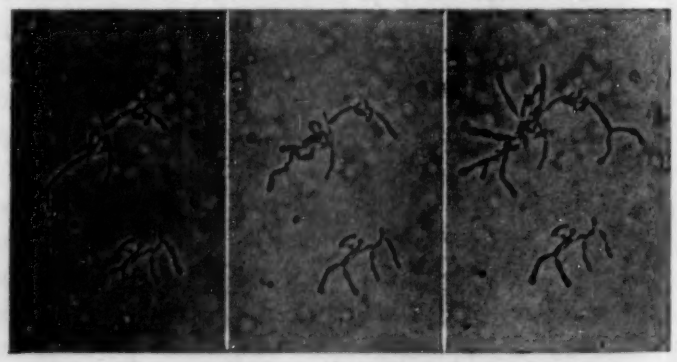

Fig. 1. Illustration of the filamentous organisms selected for microscopic study at incubation of: A, 7 hrs; B, 9 hrs; C, 13 hrs.

intervals for periods up to 33 hrs. In order to prevent this preliminary study from becoming too prolix, the experiment was limited to a relatively stable strain of the isolated organisms.

In the cultures of a single organism, the filaments were observed to divide into short bacillary bodies. Some of these in time elongated into filaments. Terminal or lateral branches were frequently found on the lengthening filaments. Occasionally a whole segment of a filament appeared to undergo autolysis, while the adjacent portion continued to proliferate. As the colony continued

to grow, through multiplication, the filamentous cells at the periphery assumed a palisade arrangement and appeared somewhat like the parallel alignment of organisms found on the tooth surface in the previously studied histological sections. We presume this characteristic arrangement may be the result of crowding in the colony. Further observations are being made by this method on other more pleomorphic strains.

In addition to the studies already described, an attempt is being made to determine whether or not the colonies composed of coccoid and diphtheroid cells have originally developed from filamentous organisms during the period of primary isolation from the tooth scrapings. If a change from the filamentous types to other forms does occur in primary culture, it would be exceedingly difficult, by routine bacteriological methods, to distinguish these colonies from those of other oral bacteria.

As can be seen from the foregoing discussion, the preponderance of filamentous organisms in the surface plaque on enamel, together with their pleomorphism when cultured, invites speculation that the round forms seen in the initial phase of early enamel caries might result from the metamorphosis of the filamentous forms which are characteristically seen on the surface.

An attempt was made to produce caries *in vitro* with the strains of actinomycetes which were isolated from the teeth scrapings. Since it is possible to determine whether erupted human teeth are noncarious only by histological examination, they are not suitable for *in vitro* work. Likewise, the chance of contamination with other mouth organisms when removing unerupted teeth from the oral cavity, together with the scarcity of human material, causes these procedures to be highly unsatisfactory.

The method used in earlier histological studies in which rats' teeth were dissected from their crypts just prior to eruption offered what seemed to be the most ideal method for this kind of study. The Syrian hamster was selected for this phase of the experiment, since its molars are peculiarly susceptible to dental caries which more closely resemble that observed in human teeth (*3*). It was possible to obtain the molars from the maxilla in a sterile condition just prior to eruption by the following procedure:

Unerupted first and second molars of the hamster were dissected from crypts of the maxilla. The oral mucosa was first stripped off, exposing the teeth in their crypts. Following the removal of the teeth, under aseptic conditions, they were placed in Difco Proteose Peptone No. 3 broth and incubated for 10 days to establish their sterility. The cotton plugs of the tubes were replaced with sterile rubber stoppers to prevent evaporation of the broth. Following the 10-day incubation period, the broth containing the teeth was inoculated with a pure culture of the filamentous organisms. Strains obtained from the human as well as from the hamster were used for the inoculations. The tubes were then incubated for a period of 3–5 months. At 3- and 4-week intervals the broth was pipetted off and fresh broth added. The culture was examined for contamination, and the pH was measured at these intervals. It was noted that at no time did the pH of the cultures drop below 6.5.

At the termination of the incubation period the teeth were removed and placed in neutral formol in preparation for histological examination. Following fixation and decalcification, they were imbedded in nitrocellulose and sectioned serially on the microtome to a thickness of 4 μ. The sections were then stained after several bacteriological methods. To date, the histological preparations of only two of these infected teeth have been completed because of the process involved.

Molar I was inoculated with strain #80, which was obtained from scrapings of hamster teeth. This strain is highly pleomorphic. The viscid sediment which develops in the broth completely enveloped the tooth and seemed to adhere loosely to it. The pH of this culture was 6.5 on the occasions when it was tested. After two months incubation, the tooth began to undergo a slight brownish discoloration. The discoloration was in contrast to the control teeth, which were not inoculated. This tooth was removed from the culture on the 74th day and placed in the fixative agent. The histological examination showed a dense intertwining mat of filamentous cells on the surface of the tooth and around the remnants of the ameloblastic layer which is adherent to the enamel sur-

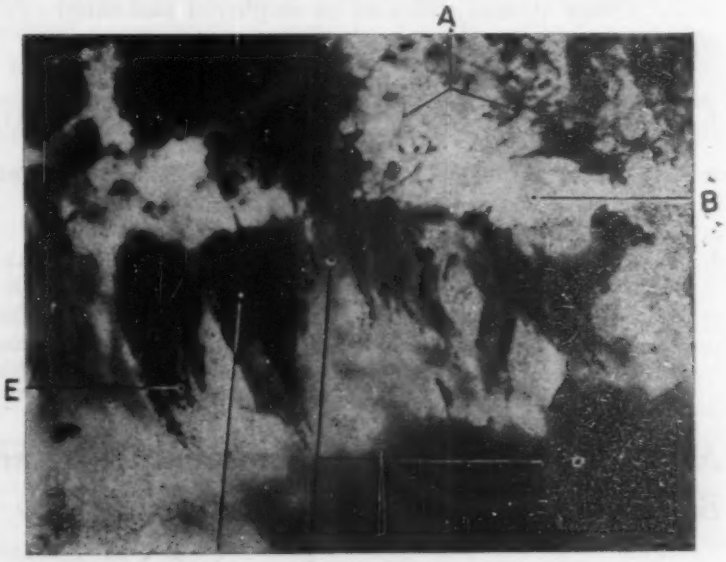

FIG. 2. Photomicrograph of a serial section taken from *in vitro* studies in which a hamster molar was infected from a pure strain of filamentous organisms. 5 μ neutral formol fixation MacCallum's Gram × 1,000. A—Filamentous organisms in the ameloblastic layer. B—Artifact due to separation. C—Uninvolved enamel matrix. D—Infected enamel undergoing degradation. E—Organisms penetrating deeply into the enamel. Note the spheroidal-appearing bodies occupying a position well in advance of areas of general breakdown.

face (Fig. 2, A). Many filaments were observed to project down into the enamel rods and interrod intervals for considerable depths. In some positions the organisms involved rods far ahead of the area of general breakdown. The irregular round bodies were especially numerous in these zones (Fig. 2, E). The rod matrix adjacent to the organisms exhibited an intense acidophilic staining reaction. In general, the picture was identical in every way to that observed in human caries and caries

in the Syrian hamster *in situ*. The organisms penetrate along selected channels and appear to invade and utilize the organic matrix in satisfying their metabolic requirement.

Molar II was inoculated with strain #82, isolated from scrapings of a microscopic human carious lesion. This strain was also highly pleomorphic. The pH of the culture, when tested, was in the neighborhood of 7.1. On the 75th day of incubation the molar was removed from the culture and placed in the fixative. An examination of the culture at this time showed it to be contaminated. It is presumed that the contamination occurred when the broth was changed 5 days earlier, since it was uncontaminated at that time. In the histological preparation of this tooth a considerable amount of the matrix was lost. The fragments which were recovered, however, exhibited a penetration by filamentous forms similar to that seen in Molar I.

It is admitted that the *in vitro* experiments to date are too few to make a definite conclusion, but we feel that the studies advance a method by which further studies may be conducted. The observations indicate that there may be an etiological relationship between the oral actinomycetes and caries of the enamel. The *in vitro* work is being repeated, using the same strains of organisms. Other strains will also be employed and other oral bacteria will be tested by the above method.

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A Paradoxical Zone Phenomenon in the Bactericidal Action of Penicillin *in Vitro*

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If varying concentrations of penicillin are added to suspensions of bacteria *in vitro*, and if at intervals thereafter one determines the number of organisms surviving at each concentration, one usually finds that the susceptibility of the particular organisms can be defined in terms of three concentrations of penicillin: (1) the concentration which serves only to reduce the rate of multiplication, (2) a somewhat higher concentration at which the organisms die faster than they multiply, with a slow decrease in the number of viable organisms, and (3) a maximally effective concentration, which varies between 2 and 10 times the "sensitivity level" of the organism as ordinarily defined. At this optimal concentration of penicillin the organisms are killed at a maximal rate which is not further affected even by a 20,000-fold increase in the concentration of the drug.

These relationships are illustrated in Table 1 for the C-203 strain of *Streptococcus pyogenes*. Different species of bacteria, and different strains of the same species, vary with respect to both the effective concentrations of penicillin and the maximum rate at which the organisms can be killed. Qualitatively, however, with most strains so far studied, there is a maximally effective level as defined above.

Paradoxical and as yet unexplained results have been obtained with certain strains of streptococci and staphylococci. With these strains there were the same three critical concentrations of penicillin, including a concentration at which the organisms were killed at a maximal rate. With further increase in the concentration of penicillin, however, the rate of bactericidal action did not remain constant as it did with, for example, *Treponema pallidum*, *Diplococcus pneumoniae*, and the group A strains of *Streptococcus pyogenes* so far tested, but instead was strikingly reduced. This is illustrated by the experiment of Table 2, carried out with the Smith strain of *Staphylococcus aureus*. In that experiment, after, for example, 6 hrs exposure to penicillin at varying concentrations, there were 400 times as many viable organisms at a concentration of 2,048 μg/cc than there were at the optimum concentration of 0.096 μg/cc, and it required 27 hrs instead of 5 to kill 99.9% of the organisms.

To test the regularity of this phenomenon, 13 strains of β-hemolytic streptococci (Lancefield groups A, B, C), 7 strains of *Str. faecalis*, 4 other strains of α-hemolytic streptococci, 7 strains of *Staph. aureus*, and 2 strains of *Staph. albus* were tested by the same technic.

Five of the 7 strains of *Str. faecalis* were rapidly killed at an optimal concentration of 4 μg/cc, at which 99.9% of the organisms were rendered nonviable in 5–7 hrs. All 5 of these strains were killed much more slowly at higher concentrations of penicillin. Thus, at 512 μg/cc it required 36–46 hrs to kill 99.9% of the organisms, instead of 5–7 hrs. This zone phenomenon was equally apparent if the results were expressed in terms of the proportion surviving after, for example, 6 hrs. Three of the other 4 strains of α-hemolytic streptococci tested showed a similar zone.

Of the β-hemolytic streptococci, the 5 group A strains failed to show the zone phenomenon. However, all 4 of the group B strains, and 2 of the 4 group C strains tested, showed a zonal susceptibility to penicillin resembling that illustrated in Table 2. Three of the 7 strains of *Staph. aureus* tested, and 1 of the 2 strains of *Staph. albus* showed the zone phenomenon in varying degree.

The paradoxically reduced bactericidal activity of penicillin in high concentrations was not due to the appearance of resistant strains at the higher concentrations. With *Str. faecalis*, the last few organisms surviving from an initial inoculum of approximately 1,000,000/cc, when subcultured and tested by the same technic as the original strain, proved to have the same resistance as the original culture, judged either by the effective concentrations of

[1] With the technical assistance of Arlyne D. Musselman.

penicillin or by the rate of death at the optimal concentration; and with such cultures there was the same zone of diminished activity at high concentrations of penicillin. The similar survivors in the case of the Smith strain of *Staph. aureus* were significantly more resistant than the original strain, but did not differ in this respect from rate at which the organisms were killed at high and low concentrations of penicillin.

The phenomenon here described may be of therapeutic significance if it should prove that, *in vivo* also, high concentrations of penicillin are less actively bactericidal against certain strains of staphylococci and streptococci than are lower concentrations of the drug. When penicillin in aqueous solution is injected intramuscularly, the optimal concentration would be present in the tissues for a relatively short period of time. Immediately after the injection, the penicillin might be present in concentrations far exceeding this optimal concentration, and correspondingly less active; because of the speed with which penicillin disappears from the blood and tissues, the optimal concentration would be present for a relatively brief period; and as soon as the penicillin level in the tissues falls below that optimal concentration, the rate of bactericidal action would be correspondingly reduced. With such strains, the most effective method for the administration of penicillin might well be a continuous intravenous or intramuscular infusion at a rate designed to maintain, at the foci of infection, concentrations of penicillin approximating the maximally effective level for the particular organism.

TABLE 1

EFFECT OF THE CONCENTRATION OF PENICILLIN G ON THE RATE AT WHICH *Str. pyogenes* (C-203) IS KILLED *in Vitro**

Time at 37°C (hrs)	Concentration of penicillin (μg/cc)									
	0	0.004	0.006	0.008	0.012	0.016	0.024	0.032	0.064	512
	% of organisms surviving (referred to original inoculum as 100)									
1½	.....	.....	....	.....	10.0	0.88	0.28	0.12	0.063	0.04
3	3,300	1,400	680	100	1.0	0.03	0.02	0.013	0.008	0.007
6	15,000	1,700	21.6	4.7	0.02	0.006	0.0038	0.003	0.002	....
12	.....	.....	....	0.024	0.0012	0.0003	0.00015	0.00015	0	....
24	4,500	15.3	0.5	0.002	0	0	0	0	....	....
Time required to kill 99% of organisms (hrs)		> 24	> 24	11	4.8	2.5	2.2	1.9	1.4 ±	1.4 ±

* Original inoculum = 750,000/cc (by colony count).

organisms which had survived the low optimal concentration of 0.064–0.128 μg/cc.

The diminished bactericidal activity in the presence of excess penicillin was not due to the production of free penicillinase. The supernatant fluid from bacterial suspensions exposed to high concentrations of penicillin for 12 to 24 hrs contained as much penicillin as an uninoculated control tube, similarly incubated. Further, if strains of *Staph. aureus* or of *Str. faecalis* were cultured in the presence of amounts of penicillin so small as not to prevent multiplication, that minimal concentration of penicillin was found to have been unaffected even after cultivation for 24 hrs, again as compared with an uninoculated control tube under similar conditions of incubation.

The zone phenomenon was found to be related to the number of organisms inoculated. The larger the inoculum, the more pronounced was the difference in the

TABLE 2

EFFECT OF THE CONCENTRATION OF PENICILLIN G ON THE RATE AT WHICH A STRAIN OF *Staph. aureus* IS KILLED *in Vitro**

Time at 37°C (hrs)	Concentration of penicillin (μg/cc)									
	0	0.024	0.032	0.048	0.064	0.096	0.128	0.25	1.0	4.0	2,048
	% of organisms surviving (referred to original inoculum as 100)										
3	12,500	200	240	27	6.4	0.8	0.56	1.1	16.4	16.6	12.0
6	11,500	230	42	0.06	0.045	0.03	0.036	0.34	5.2	9.0	12.5
12	19,800	....	0.19	0.0036	0.0038	0.0032	0.0054	0.043	0.8	1.25	1.5
24	37,100	340	280	0.031	0.075	.....	0.0005	0.0014	0.021	0.022	0.15
48	40,300	1,530	865	.....	.....	.....	0.00013	0.00026	0.00026	0.00013	0.0011
Time required to kill 99.9% of organisms (hrs)		....	13 ±	5.8	5.5	5	5	9.5	19	20	27

* Original inoculum = 2.7×10^6/cc (by colony count).

IN THE LABORATORY

Time-saving Apparatus for Respiratory Exchange Measurements[1]

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The apparatus here reported was designed originally to provide light-weight equipment for measuring the respiratory exchange of large farm animals, especially horses and mules. However, certain features of the design may be of general use in respiratory studies.

The major modification in this open-circuit apparatus is the use of a "flowrater"[3] instead of the usual displacement meter to measure pulmonary ventilation rate.[4] As pulmonary ventilation rate is affected by nervousness, the accuracy with which the resting or basal rate is measured depends not only on the mechanical precision of the meter but also on the relative level or changing rate during the period of measurement. With the displacement type meter, an interval of several minutes must be allowed between the initial and final readings of the meter; but animals, as a rule, are not quiet for several minutes at a time, and changes in rate escape detection since the rate cannot be calculated until after the final meter reading is made. The flowrater as here used, however, indicates visually at all times the state of constancy or change in the pulmonary ventilation rate, and so permits rapid measurements to be made during brief quiet periods.

Constancy of the pulmonary ventilation rate during the measurements is of considerable physiologic importance, since the composition of the expired air, the respiratory quotient (hence, the calorific values of oxygen and carbon dioxide), and the pulmonary vaporization rate are all affected by changes in the pulmonary ventilation rate.

Since the float in the flowrater tended to rise and fall with each exhalation, it was necessary to design auxiliary equipment to maintain a constant rate of flow through the flowrater. A diagram of the apparatus is shown in Fig. 1. The subject draws fresh air through the inspiration check valve (one-way valve) into the mask. Exhaled air passes from the mask through the expiration check valve and into the large expansible mixing (Douglas) bag. When the blower is running at the proper speed to draw air from the mixing bag at the same average rate at which the exhaled air enters the bag, the electrical contact, attached to the movable side of the bag, fluctuates only a small distance with each exhalation and remains on the middle post of the three stationary contacts. However, if the pulmonary ventilation rate changes sufficiently to cause an appreciable change in the volume of air in the bag, and consequently to swing the movable contact over to one of the side stationary posts, the electrical resistance in the blower motor circuit will vary in such a direction as to cause an overcompensation in the adjustment of flow into and out of the mixing bag. The movable contact will then oscillate between the center stationary post and one of the outer stationary posts, the condition of disequilibrium being signaled by the rise and fall of the float in the flowrater. Equilibrium can then be restored by adjustment of the hand rheostat.

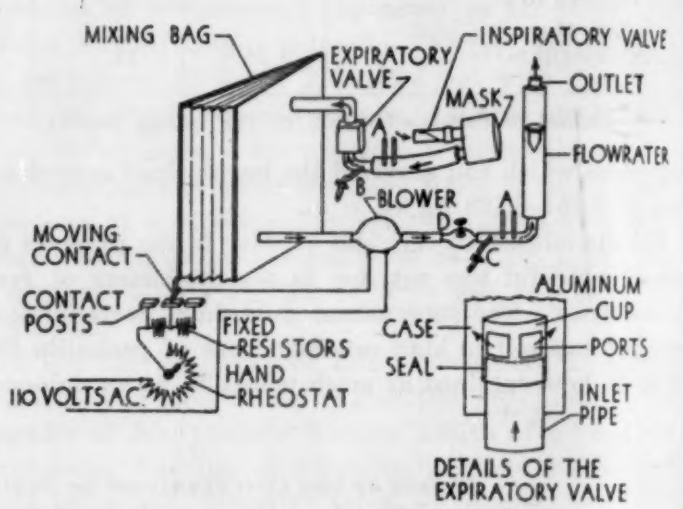

FIG. 1. Diagram of respiratory exchange apparatus. The parts designated by letters are as follows: A, wet and dry bulb thermometers; B, connection for use in recording respiration rate; C, connection for collecting samples of expired air; D, auxiliary regulating valve.

A sample of expired air is collected at C (Fig. 1) when the animal is quiet and the pulmonary ventilation rate is constant. The composition of the sample is then determined by means of laboratory gas analysis apparatus.

Various types of check valves may be used to govern the direction of flow. Since light-weight rubber valves deteriorate rapidly when exposed to expired air, we have constructed an aluminum expiratory valve (see detail,

[1] Missouri Agricultural Experiment Station Journal Series No. 1071. Partial financial support was furnished by the Bureau of Animal Industry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] With the technical assistance of Orley Miller.

[3] The flowrater (formerly called "rotameter") is a flow rate metering instrument in which the medium being measured flows between the periphery of the head of a float and the inside wall of the tapered tube in which it travels. The float remains at a constant elevation for a given rate of flow and changes elevation when the rate of flow is changed. Our instrument was manufactured by Fischer & Porter Company, Hatboro, Pennsylvania; for technical information see their catalog 98-Y, "Theory of the Rotometer."

[4] Pulmonary ventilation rate is a measure of the volume of air inspired or expired per minute.

Fig. 1) consisting of an aluminum cup inverted over the end of the pipe that transports expired air to the valve. With each exhalation the cup rises until the ports in its sides open above the end of the pipe. The succeeding inhalation pulls the valve closed. The rubbing surfaces are machined to a close fit; a film of oil between the cup and the pipe insures a tight air seal. The valve is encased in an air-tight box.

A flap-type valve with aluminum frame and rubber diaphragm is used for the inspired air. Silverman and Lee (*1*) have recently described a similar valve and have given the reference sources.

Reference

1. Silverman, L., and Lee, R. C. *Science*, 1946, **103**, 537.

Comparison of the Determination of the Disintegration Rate of Radiophosphorus by Absolute Beta Counting and Calorimetric Measurement[1]

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The quantitative measurement of radiophosphorus, P^{32} (14.3 days), is important in connection with clinical treatment and in connection with medical and biological research where the absolute quantity of beta radiation emitted by P^{32} must be known. Accordingly, it is desirable to be able to make quantitative measurements which are reasonably accurate. Up to the present, however, there has often been a great deal of uncertainty in the measurement of this material and, for that matter, in the measurement of many other radioisotopes. Curtiss (*1*) has recently pointed out that, in an interlaboratory comparison of measurements of I^{131}, deviations from the average by as much as 40–80% occurred.

We have had occasion to make a comparison of the determination of the disintegration rate of P^{32} by calorimetric measurement and by absolute beta counting and believe it is worth while to report these results in order to give an idea of the accuracy with which radiophosphorus can be measured.

The calorimeter used for the determination of the rate of heat evolution of radiophosphorus was of an isothermal type operating at the temperature of liquid nitrogen and using the rate of evaporation of nitrogen at constant pressure as the measure of the rate of heat input. A calibration of the calorimeter was made with a resistance heater at 5 points between the energy inputs of 0.2×10^{-4} and 2.5×10^{-4} watts. Mean deviation from the root mean square best straight line of rate of energy input versus nitrogen evolution was ±0.8%. Time of equilibration in passing from one heat input to another was less than 30 min.

Absolute beta counting was done with an end-window G-M counter which was calibrated using several different isotopes (Co^{60}, I^{131}, Au^{198}, RaE, Na^{24}, and UX_2) of known disintegration rate to determine the counter efficiency.[2] The disintegration rate of RaE was determined by making an absolute alpha count of RaF, which grows in as RaE decays. The disintegration rate of an equilibrium UX_1–UX_2 mixture carried from a solution of aged uranium was calculated from the known disintegration rate of the uranium. Disintegration rates of Co^{60}, I^{131}, Au^{198}, and Na^{24} were determined using coincidence counting technique.

A carrier-free sample of P^{32} prepared by the (n,p) reaction with S^{32} of an activity of approximately 25 mc was placed in the calorimeter and the energy output determined. Making a 1.3% correction for loss of beta-particle energy, which escaped the calorimeter as Bremsstrahlung, the sample measured $8.58 \pm 0.11 \times 10^{-5}$ watts at a given reference time.

A similar P^{32} sample was analyzed in a thin lens-type beta-ray spectrometer using a 50-μg/cm² source mounting. Under these conditions the Kurie plot was straight from the maximum energy to ca. 100 kv, where the absorption in the counter window could no longer be neglected. Assuming the Kurie plot to be straight below this energy, P^{32} was found to have an average energy of 0.700 Mev. This value of the average energy combined with the wattage determined calorimetrically gave a disintegration rate of $7.73 \pm 0.10 \times 10^8$ d/s at the reference time.

Absolute beta counts were made of 8 different aliquots of the P^{32} solution. A 1.3% correction for backscattering from the 2.5 mg/cm² polystyrene film on which the P^{32} aliquots were mounted for beta counting was made. The determinations showed a standard deviation of 2.1% with a value of $7.90 \pm 0.17 \times 10^8$ d/s at the reference time.

The rates of disintegration of two aliquots of the P^{32} solution were also determined by beta counting, using a National Bureau of Standards RaD + E beta-ray standard and following the procedure recommended by the Bureau. The two determinations gave disintegration rates of 7.64×10^8 and 7.83×10^8 d/s, respectively, at the reference time.

The disintegration rates determined by the calorimetric method, the use of a calibrated G-M tube, and the use of a National Bureau of Standards RaD + E beta-ray standard all agree within experimental uncertainty. The results indicate that, using thin, end-window G-M counter tubes with proper technique, the disintegration rate of P^{32} may be determined with a probable error of no more than 2 or 3%.

Reference

1. Curtiss, L. F. *Science*, 1947, **106**, 302.

[1] This document is based on work performed under Contract No. W-35-058-eng-71 for the Atomic Energy Project at the Clinton Laboratories.

[2] Reported in a paper, "Absolute Beta Counting Using End-Window Geiger-Müller Counter Tubes," by L. R. Zumwalt, presented at the September 1947 meeting of the American Chemical Society, New York City.

The Infrared Emission Spectra of CO_2 and H_2O Molecules

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Nearly all the energy radiated from the Bunsen flame arises from transitions between the energy levels of the molecules of water vapor and carbon dioxide. In order to check the validity of various theories of combustion, it is highly desirable to know the relative amount of energy which is radiated during the various transitions. In Gaydon's book, *Spectroscopy and combustion theory*, the suggestion is advanced that the energy radiated by the flame may arise from chemical rather than thermal processes. This suggestion is based, in part, on the uncertainty of the existence of certain emission bands in the 15-μ region of the infrared spectrum which should be produced by allowed energy transitions of the CO_2 molecule. Many investigators have not been able to detect radiation in this region. Actually, energy was observed in the infrared region of 15 μ by Rubens and Aschkinass (*1*) in 1898. They observed the energy from the Bunsen flame and also from heated carbon dioxide gas. Their studies on the emission of water vapor and CO_2 were of high quality, but because other workers failed to find sufficient energy for measurement in the 15-μ region, their experimental data have not been fully accepted.

During the past two years the Radiometry Unit of the National Bureau of Standards has been engaged in a study of the emission of infrared radiation from flames. This study is being conducted by the writer and other members of the staff. In the work at the Bureau the CO_2 radiation at 15 μ has been detected in the Bunsen flame, confirming the observations of Rubens and Aschkinass. The radiation consists of two emission bands occurring at 14 and 15 μ. These bands have been observed in the Bunsen flame while burning either manufactured or natural gas.

In addition to the two emission bands of CO_2, there are a number of emission lines of water vapor. It would not have been possible to identify the CO_2 bands from the array of bands in the 15-μ region if the emission of CO_2 had not been previously measured from the flame of burning CO in air. During the war the writer made the measurements of CO_2 radiation at the University of Michigan in connection with some confidential industrial work. In Fig. 1 these results are given for the first time. A grating with 1,200 lines/inch was used in the spectrometer and a KBr foreprism was used for separating the various orders. The graph indicates the amount of energy emitted by CO_2 produced by burning CO in the air. Two regions of the spectrum were found, 14 and 15 μ, where the energy was relatively intense. The 15-μ maximum has a side band on the short wave length side. These three regions of emitted energy, $(10^{0}0)$ to $(01^{1}0)$, $(02^{2}0)$ to $(01^{1}0)$, and $(01^{1}0)$ to $(00^{0}0)$, correspond to the transitions between known energy levels of the CO_2 molecule. These transitions produce bands with frequencies of 721 cm^{-1}, 668 cm^{-1}, and 667 cm^{-1}. The transition $(10^{0}0)$ to $(01^{1}0)$ shows that one of the energy levels of the inactive frequency of CO_2 changes at the same time as an active frequency, and radiation occurs. This inactive frequency may also lose energy by other transitions and collisions of the molecule with others. Some energy was observed in the entire region from 13 to 17 μ. However, as stated above, the two strongest regions of radiation were observed at 14 and 15 μ. There are other allowed transitions between energy levels which produce bands in this region. Also, it may be possible to find a band at 647 cm^{-1} for the $C^{13}O_2{}^{16}$ molecule.

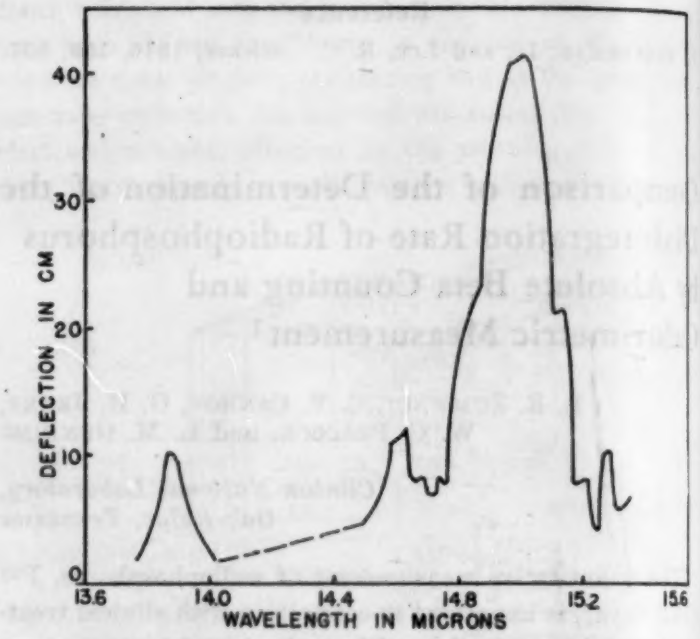

FIG. 1. The infrared emission of the CO_2 molecule in the regions of 13.9 and 15.0 μ.

Why were Rubens and Aschkinass able to observe this radiation of the CO_2 molecule at 15 μ, and, up to the present time, other observers have not been able to do so? The answer is that Rubens and Aschkinass used a KCl prism, which does not absorb in the 15-μ region. The absorption of a NaCl prism reduces the energy so much that it is difficult to detect the small amount of transmitted energy. Others could easily have observed the CO_2 radiation had they used a KCl or KBr prism. This was discussed in a paper by the writer, read before the Optical Society of America meeting in Cincinnati, October 23–25, 1947, and slides were shown comparing the energy in the 15-μ region as measured with NaCl and KBr prisms.

Considerable additional experimental data have been obtained which will be reported in a paper scheduled to appear in the February issue of the *Journal of Research of the National Bureau of Standards*. These include certain bands which are attributed to hydrocarbons. In the region between 2.8 and 3.1 μ, 15 rotational lines, which were equally spaced and separated by 22 cm^{-1}, were observed. Many lines which are a part of the rotational spectrum of the H_2O molecule were observed in the region between 12 and 24 μ.

Reference

1. RUBENS, H., and ASCHKINASS, E. *Ann. Phys. Chem.*, 1898, **64**, 584.

Book Reviews

General chemistry: an introduction to descriptive chemistry and modern chemical theory. **Linus Pauling. San Francisco: W. H. Freeman, 1947. Pp. viii + 595. (Illustrated.) $4.25.**

This contribution of Pauling to instruction in general chemistry is one of the most interesting and stimulating books to appear in the field for many years. Its directness and freshness of approach are further enhanced by the excellent illustrations of Roger Hayward (illustrator for Strong's *Procedures in experimental physics*).

The means by which Pauling has presented the subject of general chemistry is probably best shown by including a list of chapter titles, in spite of the reviewer's aversion to such a practice. The titles are, in sequence (reviewer's italics): Chemistry; Nature and Properties of Matter; *Atoms, Molecules, and Crystals*; Elements, Elementary Substances, and Compounds; *Chemical Elements and the Periodic Law, Parts 1 and 2*; Weight Relations in Chemical Reactions; *Ions, Ionic Valence, and Electrolysis*; *Covalence and Electronic Structure*; Oxidation-Reduction Reactions; Chromium and Manganese, and Related Metals; Halogens; *Laws of Electrolysis, Electrolytic Processes*; *Properties of Gases*; Water; Properties of Solutions; Sulfur; Nitrogen; *Rate of Chemical Reactions*; *Chemical Equilibrium*; *Acids and Bases*; Phosphorus, Arsenic, Antimony, and Bismuth; Solubility Product and Precipitation; Complex Ions; Copper, Silver, and Gold; Zinc, Cadmium, and Mercury; Iron, Cobalt, Nickel, and the Platinum Metals; Tin, Lead, and Other Metals; Organic Chemistry; *Chemistry of Silicon*; Thermochemistry; Oxidation-Reduction Equilibria; Radio-chemistry.

In particular, it will be noted that the subject of chemistry is introduced by discussing the properties of substances in terms of atoms and molecules, and the development of the subject follows in as logical an order as possible, without respect to historical precedence. The chapter entitled *Atoms, Molecules, and Crystals* is a very pleasing example of the reasonableness of this approach, it being much easier for the beginning student to understand how matter is built up from atoms and molecules when they are held in a relatively stationary condition than when they are moving about randomly. Following this same reasoning, the properties of gases are not presented until Chapter 14. Electrolysis and electrode reactions are considered first in Chapter 8 for molten salts, without the complication of a solvent being present and taking part in the electrode processes, electrolysis in solutions following later. The detailed consideration of acids and bases is presented in Chapter 21, after the student is prepared for the concepts introduced. Throughout the text, where the historical background is important in itself or serves to illustrate the scientific method, it is included following the logical presentation of the subject.

No previous instruction in chemistry is assumed of the student, and each new term is defined as it is introduced. Students who have previously had high school chemistry will, nevertheless, find this book a challenging and exciting experience. Although Pauling claims that descriptive chemistry is presented in a limited amount ("... enough to provide ... an introduction to the multitude of chemical substances, but not so much as to confuse ..."), the chemistry of the elements and their compounds is discussed in sufficient detail and integrated so well with atomic and molecular structure and the periodic table, that a broad knowledge of fundamental chemical facts should be retained by the student. At the end of each chapter are a section entitled "Concepts and Terms Introduced in This Chapter" and a set of thought-provoking exercises, both of which allow the student to test his mastery of the textual material.

Occasionally new and difficult ideas are perhaps introduced in too close order. An extreme example of this (by no means typical) occurs on page 67 in defining the word *acid*. Another criticism is the treatment in the text of elements of atomic number 90–96 as transition elements, even though they are properly classed as a second rare-earth group in the periodic tables presented. The text would be much more useful for the elementary student if it were more completely indexed.

Regarding the physical make-up of the book, the typography and composition are excellent, but the binding is not reinforced and is poor. The reviewer found very few errors in typography, and only one compositor's mistake, which is a splendid record for a first printing of a first edition. This is the first volume from this new publisher to come to the reviewer's attention, and sets a high standard for subsequent publications.

J. S. COLES

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Gas turbines and jet propulsion for aircraft. **(4th ed.) G. Geoffrey Smith. New York: Aircraft Books; England: Flight Publishing Company, 1946. Pp. viii + 256. (Illustrated.)**

In his fourth edition of *Gas turbines and jet propulsion for aircraft*, G. Geoffrey Smith attempts to bring to light some of the major accomplishments achieved in this field in the last 5 years. With this type of propulsion fast replacing the reciprocating engines in the present military airplanes, a text containing general knowledge of the subject is most timely. The author, who has dealt with aero-engines for a great many years and who is one of the best authorities on their history and development, is well qualified to be one of the first to present such a text to the public.

The author includes not only British developments but also those of the rest of Europe and America. A great many excellent illustrations of the basic physical concepts,

comparative tables, component parts, finished units, and specific applications make this book readily understandable to the layman and pilot, as well as the engineer. Quotations from papers delivered by aeronautical and turbine engineers have been freely cited to provide a broad survey of the trend of thought and progress.

The text contains chapters on Jet Propulsion, Thrust and Performance, Early Projects, Gas Turbine Components, Combustion Systems, Metallurgy, British Gas Turbines, American Gas Turbines, German Gas Turbines, Testing and Maintenance, Types of Turbine-propelled Aircraft, Jets Versus Airscrews, Turbine-Airscrew Projects, Aerodynamic Problems, Tailless Aircraft and the Flying Wing, Closed-Cycle Gas Turbines, Steam Turbines, Guided Missiles and Flying Bombs, Official Adoption of Jet Aircraft, Broadcasting the News, and Notable Views on Turbine Propulsion. The ease and simplicity, as well as the completeness, with which this book was written is indicative of the authoritative source of the information it contains.

ROBERT S. ROSS

Case Institute of Technology

Introduction to electron optics: the production, propagation, and focusing of electron beams. V. E. Cosslett. Oxford, Engl.: at the Clarendon Press, 1946. Pp. x + 272. (Illustrated.) $6.50.

This book provides an excellent text or reference for a third- or fourth-year course in either electron optics, electronics, or physics where the subject matter is directed toward the understanding of the production, propagation, and focusing of beams of ions and electrons.

Essentially, in the reviewer's opinion, this book is divided into two parts. The first part, which includes the first 5 chapters, deals with a clear and concise theoretical exposition on the electrostatic field, electrostatic focusing, and magnetic focusing. Chapter V presents a trigonometrical approach to the subject of image aberrations. The appendix presents the Hamiltonian Method in Electron Optics.

With a background in calculus, partial differential equations, and an understanding of scalar and vector products as well as Bessel functions, the student or reader should gain a complete physical and mathematical understanding of the effect of electric or magnetic fields on the trajectory and focusing of an electron beam. As the author claims, the mathematical exposition is kept subordinate to the description of the physical principles. In many cases overlapping exists when first a phenomenon is explained physically and later the same phenomenon is presented mathematically. This method of presentation makes the subject matter more easily understood.

The approach to the subject of electron optics in this book is similar to geometric light optics. The optical analogy is made frequently, which enables the reader, who may have a knowledge of light optics, to gain a clearer picture of the electron system.

The second part of the book, the last 5 chapters, deals with devices in which the principles of electron optics are applied. First, the factors involving the production of an electron beam are presented. The theories on thermionic emission (centered around Richardson's equation) are discussed; the structures of various electron guns are clearly illustrated and described. In this chapter, photoelectric emission and electron multipliers are described.

In the following chapters, the cathode-ray tube, television pickup tubes, both those in the iconoscope and orthicon family, with the methods and theories used to effect the deflection of the electron beams within the tubes, are clearly presented with a minimum of mathematics. The whole of Chapter VIII is devoted to the electron microscope and gives a clear and precise picture of how the principles of electron diffraction are used in electron microscopy. The remaining two chapters deal with cylindrical fields of the type that are found in a magnetron or cyclotron and velocity-modulated beams of the type that are encountered in a Klystron. The functions of the magnetron, cyclotron, and Klystron tubes are clearly analyzed and illustrated.

It is believed that the extensive bibliographies, which are found at the end of each chapter, will be extremely helpful to those readers who wish to delve more deeply into the subject matter.

JACK KLINE

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Scientific Book Register

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VAN DEN BROEK, J. A. *Theory of limit design.* New York: John Wiley; London: Chapman & Hall, 1948. Pp. viii + 144. (Illustrated.) $3.50.

VISHER, STEPHEN SARGENT. *Scientists starred 1903–1943 in "American men of science." a study of collegiate and doctoral training, birthplace, distribution, backgrounds, and developmental influences.* Baltimore: Johns Hopkins Press, 1947. Pp. xxiii + 556. $4.50.